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SUBACUTE BACTERIAL ENDOCARDITIS TREATED UNSUCCESSFULLY WITH SULFAPYRIDINE

A Report of Five Cases

JACK KINELL, M.D. and A. CARLTON ERNSTENE, M.D.

Recent medical literature has contained a few reports of the successful treatment of subacute bacterial endocarditis with sulfanilamide or sulfapyridine. The most encouraging of these have been the reports of Kelson and White¹ and of Major². Recovery occurred in three of seven cases treated by Kelson and White with sulfapyridine and heparin in combination and in three of seven cases treated by Major with sulfanilamide or sulfapyridine alone. Stimulated by these reports, we have employed sulfapyridine in the treatment of five patients with subacute bacterial endocarditis, but the results have been uniformly disappointing. Two patients have died and the others are unimproved. Streptococcus viridans was the responsible organism in two of the cases, while a non-hemolytic streptococcus was found in two others, and in the fifth case an anaerobic streptococcus was recovered.

CASE REPORTS

Case 1: A white boy, eighteen years of age, was admitted to the hospital on November 1, 1939 because of chills, fever, and sweats, one week in duration. The onset of symptoms had been sudden and there had been no recent acute illness. The past medical history disclosed nothing suggestive of an earlier rheumatic infection.

Physical examination revealed a well-nourished individual who did not appear particularly ill. The temperature, however, was 104° F. and the pulse rate 140 per minute. The blood pressure was 148 mm. systolic and 0 diastolic. The heart was not enlarged and its rhythm was regular. A prolonged diastolic murmur was present over the aortic area and was transmitted down along the left sternal border and to the apex. A small splinter hemorrhage was found in the nail bed of one finger and another small petechia was present on another finger. The spleen and liver were not palpable. Blood cultures taken on the first and second hospital days yielded growths of streptococcus viridans within 48 hours. A diagnosis of rheumatic heart disease with aortic insufficiency and subacute bacterial endocarditis was made.

Sulfapyridine was started on the third hospital day. Seven grams of the drug were administered during the first twenty-four hours and 6 grams were given every twenty-four hours thereafter. This dosage maintained a sulfapyridine level in the blood of 4.5 mg. to 5.0 mg. per 100 cc. The temperature fell to normal within twenty-four hours and remained normal until the time of discharge on the ninth hospital day. A blood culture taken on the day of discharge remained sterile.

Sulfapyridine was continued in doses of 1 gram every four hours day and night, under the supervision of the patient's physician. Except for a transient rise to 102° F. a few days after returning home, the temperature remained normal. Three blood cultures taken three weeks later remained sterile. The dosage of sulfapyridine was then reduced to 1 gram every six hours. Two weeks later the

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temperature again started rising to 100° to 100.5° F. every afternoon. Blood cultures taken on December 30 were again positive for streptococcus viridans. The patient was instructed to continue with his medication although it was felt that a sufficient amount had been given for an adequate therapeutic trial.

Case 2: A white woman, aged twenty-nine years, was admitted to the hospital on October 31, 1939 because of severe frontal headache, nausea, vomiting, chills, and fever. Thirteen teeth had been extracted one month earlier and the symptoms had developed one week after this. The patient had had rheumatic fever as a child.

Physical examination revealed slight enlargement of the heart to the left and a loud systolic murmur at the apex. The liver and spleen were not palpable and no petechiae were present. During the first two days in the hospital, the temperature rose to 102° F. and there was frequent vomiting. Blood cultures were taken and gave a growth of non-hemolytic streptococci within twenty-four hours. A diagnosis of rheumatic heart disease with mitral insufficiency and subacute bacterial endocarditis was made.

The patient was started on sulfapyridine in doses of 1 gram every four hours on the first day and 1 gram every six hours for thirty-two days thereafter. The blood sulfapyridine level varied from 1.9 mg. to 3.6 mg. per 100 cc. The temperature fell to normal within twelve hours after the first dose of the drug and remained normal until the tenth hospital day. Following this there was a gradual return of fever to between 100° and 100.4° F. every afternoon, and this continued until the patient's discharge on December 2, 1939. Blood cultures on the day of discharge were still positive for non-hemolytic streptococci.

There was no decrease in the erythrocyte or leukocyte count or in the hemoglobin level during the period of sulfapyridine therapy. No petechiae or other evidence of embolic phenomena were observed at any time. The urine contained blood on one occasion but this, of course, may have been due to the passage of acetyl sulfapyridine crystals.

Case 3: A white man, thirty-six years of age and known to have central nervous system lues and luetic aortitis with aortic insufficiency, was admitted to the hospital on October 24, 1939. Eleven days earlier severe pain had developed suddenly in the lower back and five days later pain also had developed in the calf of the left leg. The pain in both regions persisted and was still present at the time of admission to the hospital. The patient also reported that for about three months he had been having frequent night sweats.

At the time of admission to the hospital the temperature was 100.6° F., the pulse rate 120 per minute, and the blood pressure 160 mm. systolic and 30 mm. diastolic. The heart was not enlarged and its rhythm was regular. A short systolic murmur was heard at the aortic area and the second sound was followed by a long diastolic murmur. There was a moderate apical systolic murmur. The spleen was palpable two finger breadths below the costal margin. There was no tenderness over the lower spine but movements of the lower back were extremely painful. The calf of the left leg was very tender. No petechiae were seen. The erythrocyte count was 3,970,000 per cu. mm. and the hemoglobin content 65 per cent. The white blood cell count was 6,600 per cu. mm. Blood cultures taken on three successive days yielded a non-hemolytic streptococcus. A diagnosis of luctic aortic insufficiency and subacute bacterial endocarditis was made.

The patient was started on sulfapyridine in doses of 1 gram every four hours day and night, and this maintained a blood sulfapyridine level of 10.6 mg. to 15.0 mg. per 100 cc. The temperature fell to normal within twenty-four hours of the first dose of the drug, and the pain in the back and leg promptly improved.

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The temperature remained normal for nine days but two blood cultures taken during this time gave growths of non-hemolytic streptococci. Fever returned after the ninth day and the temperature eventually rose to as high as 105.6° F. Petechiae appeared in the fingers and conjunctivae, and there were repeated emboli to the kidneys, spleen, and central nervous system. After twenty-one days of sulfapyridine therapy, the leukocyte count began to decrease and, in spite of discontinuance of the drug, fell to 450 cells per cu. mm. with complete disappearance of the granulocytes. Repeated blood transfusions were of no benefit. The patient became comatose and expired on the thirty-eighth day in the hospital. Blood cultures made six days before death were still positive. Necropsy revealed aneurysmal dilatation of the proximal portion of the aortic valves with heavy vegetations on the valve cusps.

Case 4: A negro, aged fifteen years, entered the hospital on October 16, 1939 complaining of pain in the right hip. He stated that for several months he had felt generally under par and that a gradually increasing pallor of his lips had been noted. Two months before admission, the ankles had become swollen and painful and from this time on there had been a low grade afternoon fever. One month before entering the hospital, sudden severe pain had developed in the right hip, and a few days later similar pain had developed in the left hip. There was no past history of rheumatic infection.

Physical examination showed an obviously ill individual. The temperature was 100.4° F., the pulse rate 120 beats per minute, and the blood pressure 120 mm. systolic and 60 mm. diastolic. The heart was not enlarged and its rhythm was regular. At the apex a rumbling presystolic murmur was heard and the first sound was greatly accentuated. A long diastolic murmur was present at the aortic area and was transmitted down along the left sternal border. The liver and spleen were not palpable. There was marked clubbing of the fingers and toes. No petechiae were present. Movements of the right hip joint were quite painful.

The erythrocyte count was 3,380,000 per cu.mm. and the hemoglobin content 55 per cent. The white blood cell count was 11,300 per cu.mm. Blood cultures taken on four successive days yielded a streptococcus after incubation for five to seven days. Repeated attempts at identification of this organism by plating on blood agar were unsuccessful. A diagnosis of rheumatic heart disease with mitral stenosis and aortic insufficiency and subacute bacterial endocarditis was made.

The patient was started on sulfapyridine by mouth in doses of 1 gram every four hours day and night. The sulfapyridine concentration in the blood ranged from 2.8 mg. to 6.0 mg. per 100 cc. Because of severe nausea and vomiting, an attempt was made to administer the same dosage rectally but the blood sulfapyridine level fell to 1.3 mg. per 100 cc. The rectal administration of sodium sulfapyridine met with no more success. Sodium sulfapyridine was then administered intravenously in 5 per cent solution in amounts varying from 1.5 gm. to 6 gm. daily given in divided doses. During this period the sulfapyridine concentration in the blood ranged from 6.0 to 11.4 mg. per 100 cc. On the fifteenth day of treatment, and after the patient had received 70 gm. of sulfapyridine, the leukocyte count was 6,900 per cu.mm. After twenty-one days and 104.5 gm. of sulfapyridine, the white count had fallen to 1,950 per cu.mm. The drug was discontinued and the leukocyte count immediately began to rise. At no time during the course of treatment was the patient's temperature restored to normal. Blood cultures continued to yield an anaerobic streptococcus. There were repeated emboli to

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the fingers, extremities, spleen, and kidneys. Death occurred on November 24, 1939, thirty-nine days after admission to the hospital.

Case 5: A white woman, thirty-four years of age, was admitted to the hospital on December 13, 1939 because of fever, weakness, loss of weight, and palpitation, four months in duration. She had been treated with sulfanilamide (80 gr. daily) for two weeks without benefit. No history of rheumatic infections could be obtained.

On examination the heart was not enlarged and its rhythm was regular. A moderate apical systolic murmur was present. The spleen was palpable at the costal margin. No petechiae were found. The erythrocyte count was 3,760,000 per cu.mm. and the hemoglobin content 58 per cent. The white blood cell count was 5000 per cu.mm. The urine contained a trace of albumin and a few red blood cells. Blood cultures gave a growth of streptococcus viridans in seventy-two hours.

During the first three days in the hospital, the maximum temperature ranged from 101.3° F. to 103.4° F. Numerous petechiae appeared in the finger tips and under the nails. On one occasion the patient complained of sudden severe pain in the left upper quadrant of the abdomen which was interpreted as due to embolism of the spleen. Sulfapyridine was started on the third day in doses of 1 gram every four hours day and night. The temperature fell to normal within twenty-four hours. The sulfapyridine blood level quickly rose to 14.9 mg. per 100 cc. and then fell to 5.6 mg. per 100 cc. when the dosage of the drug was reduced to 1 gram every six hours. Five days after starting therapy, the patient was discharged to carry on treatment under the supervision of her own physician. Fever returned, the temperature rising to 102° to 103° F. every afternoon. On January 19, 1940, after thirty-three days of sulfapyridine therapy, blood cultures were still positive for a green producing streptococcus. The sulfapyridine blood level was 5.9 mg. per 100 cc. and the drug was discontinued.

SUMMARY

Sulfapyridine was employed unsuccessfully in the treatment of five cases of subacute bacterial endocarditis. The causative organism was streptococcus viridans in two cases, non-hemolytic streptococci in two cases, and an anaerobic streptococcus in the other. The dosage of sulfapyridine was adequate in every case according to generally accepted standards. The duration of treatment to date has varied from nineteen to fifty-seven days. Two of the patients have died. In the other three, the blood cultures have remained positive and the disease is following its usual progressive course.

- Kelson, S. R. and White, P. D.: A new method of treatment of subacute bacterial endocarditis using sulfapyridine and heparin in combination; preliminary report, J. A. M. A. 113:1700-1702, (November 4) 1939.
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VESICAL LITHIASIS CONCOMITANT WITH BENIGN ENLARGEMENT OF THE PROSTATE

F. C. SCHLUMBERGER, M.D.

It is a commonly accepted fact that urinary stasis is a requisite to the formation of bladder stones. Therefore, one would expect to find stones frequently associated with obstructive lesions at the bladder neck.

In a review of one hundred cases of vesical lithiasis seen at the Cleveland Clinic, 40 per cent were found to have been associated with benign enlargement of the prostate. This is one reason why vesical calculus occurs almost exclusively in men in this country. Only two cases of vesical calculus occurred in women in this group. Other common causes in men were primary urethral stricture, stricture of the bladder neck following prostatectomy, and diverticulum of the bladder.

Stasis of urine alone is not always enough to bring about the formation of calculi. Infection, changes in the level of the pH of the urine, and the presence of a nucleus markedly influence their formation. Infection greatly increases the rapidity of formation. Urine mixed with inflammatory exudates has, by no means, the same physical characteristics as normal urine. Clumps of bacteria, blood clots, and inflammatory exudates often form the nucleus of a stone. Sepsis produces a change in the surface tension of the urine, thus enhancing the tendency to form deposits.

Changes in the composition and pH of the urine have an important bearing on the type of calculus formed. An acid urine predisposes to the formation of calculi composed of urates and oxalates. However, a change in the bacterial flora of the urine may so alter its pH that precipitation of alkaline substances takes place. This explains the formation of laminated calculi. Blood and excessive amounts of mucus in the urine also influence the composition of the stone.

Where urinary stasis exists, only a nucleus is necessary to begin the formation of a calculus. The rapid precipitation of crystals may form a nucleus or a small stone may pass from the kidney into the bladder. When bladder calculi exist, one always should rule out their presence in the upper urinary tracts. On one occasion in our experience, the nucleus of a stone was a small piece of resected prostate gland. This, of course, emphasizes the importance of completely removing all the pieces following resection of the prostate, and maintaining the bladder free of blood clots following this procedure. This also applies to litholopaxy, because retained fragments of stone may form the nucleus of a recurrent stone.

It has also been our experience to see formation of calcarious deposits on a sloughing surface following incomplete resection of the prostate.





Figure 1: a. Roentgenogram showing multiple calculi associated with benign enlargement of the prostate.

b. Photograph of calculi removed transurethrally.

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In this case, healing of the resected prostatic bed takes place slowly and, in the presence of infection, the sloughing area becomes a ready nucleus for the deposition of crystals. Particles often break off and form free calculi in the bladder. This may be avoided by cleanly resecting the prostate, which allows healing to occur more smoothly and rapidly.

In this group of bladder stones associated with prostatic hypertrophy, multiple calculi were found in thirty-six cases and single calculi only in four cases. Multiple calculi were associated with large amounts of residual urine. Development of multiple stones in such instances is dependent upon the wide separation of minute nuclei by a large quantity of fluid which discourages the formation of a single calculus (Fig. 1). These small calculi usually are faceted or wedge-shaped and jackstones occur occasionally. The shape of the calculi is greatly influenced by the amount of tenesmus present and the compression in the bladder. Single calculi often become impacted in a deep bas fond or prostatic pouch and assume the shape of the pouch.

Considerable emphasis has been placed upon the chemical composition of calculi formed in the urinary tract. This factor has become of importance in the recurrent formation of stones and is responsible for recently advanced therapeutic measures. Chemical analysis was carried out in twenty-one of the forty cases in this group. In sixteen cases, the composition of the calculi consisted largely of calcium phosphate and calcium carbonate with traces of oxalate; in three cases the calculi were composed of urates and oxalates with traces of phosphates, and in one case the calculus consisted of oxalates alone. The precipitation of pure oxalate crystals often occurs in sterile urine. Alkaline substances are precipitated in the presence of urea splitting organisms such as the proteus bacillus, certain strains of the Staphylococcus, and colon These organisms, because of their ability to split urea, maintain the urine alkaline in reaction and facilitate the precipitation of phosphates. Thus it becomes important to make a careful culture of the bladder urine and to determine whether the organism present has the power to split urea. Following removal of the stone, one may then institute the proper dietary and medical management to maintain the urine at the desired pH in an attempt to prevent the recurrent formation of calculi.

A few characteristic symptoms often lead to a diagnosis of a stone in the bladder. However, in elderly men with prostatic obstruction, this condition sometimes gives relatively few symptoms. Often the obstructive symptoms overshadow those produced by the calculi and they may be entirely overlooked.

Severe pain and terminal tenesmus many times is a major complaint. This discomfort is usually described as a knife-like pain at the bladder

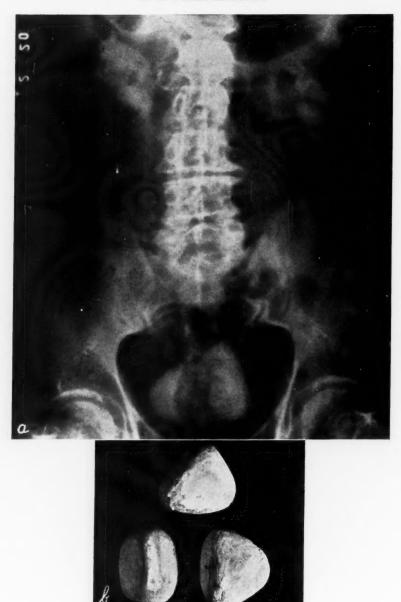


FIGURE 2: a. Roentgenogram showing three large calculi present in the bladder and the resultant ureteral and kidney disease.

b. Photograph of calculi removed by cystolithotomy.

neck and through the urethra, intensifying itself near the end of the penis. It is nearly always accompanied by terminal hematuria. Sudden cessation of the stream is a common complaint and occurs when the stone falls into the bladder outlet. The patient often states that he is more comfortable when lying down. This position, of course, allows the stone to fall back into the bladder, away from an already severely irritated bladder neck. The presence of calculi in the bladder may be definitely established by roentgenographic or cystoscopic examination. Nonopaque calculi are sometimes encountered in the bladder.

Distinct changes may occur in both the bladder and upper urinary tract due to longstanding bladder neck obstruction with calculi. The bladder wall becomes markedly thickened and heavily trabeculated. A perivesical cellulitis may develop. The ureters may become dilated and tortuous and the kidneys hydronephrotic. Ascending infection is almost inevitable and a diffuse pyelonephritis results (Fig. 2).

Two essential procedures are necessary in the treatment of this condition. First, the bladder neck obstruction must be adequately corrected and second, the stone should be completely removed. Inadequate resection of the prostate or incomplete removal of the stone predispose to recurrent formation of stones. The size of the prostatic enlargement or stone may determine the type of surgical procedure to be used. The general physical health of the patient is also of importance. Perhaps the age and general health do not warrant a time-consuming procedure such as litholopaxy might be if the stone is in the upper limits of size or of firm composition. Calculi often are removed much more rapidly by lithotomy with less harm to the patient than by difficult litholopaxy.

The condition of the bladder or upper urinary tract may demand adequate and longstanding bladder drainage which would warrant open operation and removal of the calculi. Following this, the obstructing portion of the prostate may be removed by resection transurethrally or by complete enucleation of the gland. If the obstructing prostate is of such size that relief of the obstruction can be obtained only by complete enucleation of the gland, removal of the calculi becomes very simple. Variations in the management must be applied according to the indications in the individual case.

These patients spontaneously fall into rather distinct groups according to the type of calculus present. First are those patients whose obstructive symptoms can be relieved by transurethral resection and the calculi are small enough to be removed through the sheath of the resectoscope. Nine patients of this group were cared for in this manner. Sometimes it may be necessary to employ the evacuating bulb or perhaps a grasping forceps. If the prostate is cleanly resected so that the beak of the instrument dips well down into the post-prostatic pouch which is present in so many of these cases, small calculi, as a rule, will pass spontaneously.

The second group consists of patients whose symptoms of obstruction can be adequately treated by transurethral resection, and the calculi are sufficiently large to necessitate the use of a small rongeur. These calculi are considered small but require crushing with a rongeur that can be introduced through the large resectoscope sheath. The remaining fragments may then be evacuated.

In the third group are those patients whose obstructive symptoms can be relieved by transurethral resection, the calculi being of sufficient size to require the use of a lithotrite. This procedure was carried out in twenty-four patients in this group. Two distinct procedures are necessary and may become time-consuming if both are attempted at one sitting. As in the two preceding groups, the obstructing portion of the prostate should be removed first. If time allows, litholopaxy may then follow this procedure or it may be carried out later at a second operation. Resection of the prostate is of great importance in this group and must be done first, as it facilitates the introduction and manipulation of the lithotrite. A number of instruments are available for this purpose. The visual type of lithotrite is perhaps the most applicable; however, the nonvisual Bigelow lithotrite still continues to be useful. Even though one may be skilled in the use of these instruments, this procedure may become quite involved and care must be taken not to injure the bladder wall.

The fourth group includes patients in whom the calculi are so large that litholopaxy becomes impossible, although the prostate is still amenable to resection. As a rule, complete enucleation of the gland is not warranted because of age or of general health. The calculi may be present in a diverticulum, making them inaccessible to the lithotrite. Where large calculi are present, marked infection often exists and perhaps considerable damage has been rendered the upper urinary tract. This may be alleviated by open operation and bladder drainage over a period of time. On several occasions in our series where the obstructing portion of the prostate was distinctly a middle lobe, removal of the calculi and the middle lobe of the prostate have been accomplished through a cystotomy. In such an instance, the obstructing portion of the gland is resected by means of a high frequency loop. Cystotomy and continuous drainage of the bladder simplifies transurethral resection of the prostate and often shortens considerably the convalescence of the patient.

The fifth group is comprised of those patients in whom both the calculi and the prostate are exceedingly large, or perhaps the prostate alone is very large, in which case the calculi become a secondary consideration. In this series of forty cases, prostatectomy was done in five cases. On four occasions, a one-stage suprapubic prostatectomy was performed and removal of the calculi was accomplished. In one case, a

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cystolithotomy was done and bladder drainage was established. This was followed later by a prostatectomy.

Certain contraindications to litholopaxy exist and should be observed. The presence of a diverticulum, marked trabeculation of the bladder, severe cystitis, and upper urinary tract infection are contraindications. The prostate or the stone itself may be too large. Urethral obstruction such as a stricture may prevent the use of any type of transurethral procedure. If no contraindications exist, however, litholopaxy is a very useful procedure and a boon to the patient suffering from coexisting vesical lithiasis and benign enlargement of the prostate.

SUMMARY

Urinary stasis is the most important predetermining factor in the formation of primary vesical calculi, as is evidenced by their frequent occurrence in association with prostatism. Of one hundred cases of vesical calculi, forty were found to be associated with benign enlargement of the prostate.

Variations in the findings render each case an individual problem. However, the majority of patients are amenable to transurethral resection of the prostate and litholopaxy.

Prevention of the recurrent formation of calculi is of prime importance. This may be accomplished by establishing a free flow of urine from the bladder and complete removal of the calculi. Accurate determination of the chemical constituents of the calculi should be made and adequate measures instituted to control the level of the pH of the urine.

EARLY DIAGNOSIS OF DISEASES OF THE COLON AND RECTUM

E. N. COLLINS, M.D.

In this discussion of the present status of diseases of the colon, only the practical features, which in our experience have proved helpful in early diagnosis, will be considered.

Diseases of the colon are now recognized more frequently than heretofore. This may mean that these diseases are becoming more prevalent, but, more likely, it probably indicates that the clinician is becoming more skillful in diagnosis. However, certain indispensable examinations which should be done in every patient suspected of having disease of the colon or rectum are still not being done *routinely*. The more widespread routine use of these examinations will result in a greater percentage of cured patients.

The newer developments in roentgenology during the past decade have played no little part in earlier diagnosis. In fact, the roentgen examination has become the most important single diagnostic procedure when dealing with lesions above the reach of the proctosigmoidoscope, which affect the lumenal contour of the colon.

In dealing with lesions in the lower sigmoid colon and rectum, we must remember that the findings by roentgen examination alone are not reliable. Even in this enlightened age, patients are being told that they have no organic disease because the roentgen examination was reported as showing normal findings, when a simple digital or proctosigmoidoscopic examination may reveal an obvious cancer.

Hemorrhoidectomies are still being done without making certain that a carcinoma or a polyposis above the hemorrhoids does not exist, as was the case ten years ago. Ointments and suppositories are still being prescribed without adequate examination to exclude other causes for the symptoms.

We must realize that *symptoms* pertaining to the rectum and colon are often indeterminate. Several types of lesions can cause the same symptoms. Organic abnormality cannot be excluded without doing digital and proctosigmoidoscopic examinations. The roentgen examination, using the barium enema, must, of course, be included in the *routine examination* when a lesion in the colon is suspected.

If a non-neoplastic ulcerative process in the colon is suspected, such as amebiasis, a bacillary dysentery or chronic nonspecific ulcerative colitis, stool examinations are of paramount importance, and they should be made prior to the administration of the barium enema.

The digital rectal examination is usually made in the left or right lateral position; however, when neoplastic disease is suspected and

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examinations with the patient in the usual positions result in negative findings, the knee-chest and squatting positions should be used. The bimanual method also is of considerable importance in dealing with neoplastic disease, for this may reveal the presence of an obstructing lesion in the rectosigmoid area or a "Blumer's shelf," that is, evidence of retrograde metastases in the cul-de-sac, from neoplastic disease in the digestive tract above this level.

In doing the *proctosigmoidoscopic examination*, a special table is convenient where a large number of patients are examined, but the same results are obtained without special equipment, using any of the standard scopes and having the patient in the knee-chest position, the spine and abdominal wall being allowed to fall forward.

In obtaining stools for examination, we customarily give the patient a sterilized pasteboard carton in which to collect stools during the night and early morning hours. When careful appraisal of the patient's illness leads to the suspicion of parasitic disease and not an obstructing neoplastic process, a dose of Epsom salts is given the following morning before breakfast, and the patient is instructed to report to the bacteriologic laboratory immediately after breakfast. Warm-stage microscopic examinations of the stools are made for the motile forms of parasites as soon as the stool is passed. At least three stools are examined before this examination is considered adequate. In addition to searching for the motile forms in warm stools and encysted forms in the stools brought in by the patient, any other abnormalities, such as evidence of improper digestion of fats, starches or proteins is recorded. Cultures are made in dysentery cases.

Stool examinations not only give important information relative to an ulcerative process in the digestive tract. They may give evidence of other abnormalities, such as sprue which may have resulted in a confusing clinical syndrome. On the other hand, repeated normal findings on stool examination are significant in excluding organic disease of the digestive tract.

The roentgen findings are obvious when a lesion in the colon is far advanced, but this may represent the hopeless stage. Almost any type of roentgen film will demonstrate this stage. In order to discover an early curable lesion of the colon (above the rectosigmoid region) by the roentgen examination, the patient and clinician must cooperate with the expert roentgenologist. Sufficient time and the use of certain routine procedures must be allowed so that the roentgenologist can make a satisfactory examination. Allowing adequate time for the proper preparation of the patient alone, may result in making an early diagnosis which might be missed without this precaution. A request by the roentgenologist for recheck or progress examinations should not be neglected by the clinician. We have found the following procedures most important:

1. The preparation. We know that inspissated fecal material in the colon can be mistaken for polypoid lesions. Our routine calls for giving the patient 1 to 2 ounces of castor oil on the day preceding the examination. In patients having obvious obstructing lesions, reliance is placed on cleansing enemas. If the colon is not empty at the time of the examination a more thorough preparation and recheck examination is used.

2. The careful *fluoroscopic* examination by the physician radiologist himself. Many patients bring in films of the colon made after an X-ray technician or a nurse has given a barium enema. Such films may, of course, reveal the presence of an advanced lesion but they do not, by any means, exclude the possibility of an early lesion which is covered by a redundant loop of colon. On the other hand, a simple spasm may have been interpreted as a carcinoma. During the fluoroscopic examination, the physician radiologist observes every segment of the colon as it fills, while the patient is turned into the most advantageous positions. flow of barium suspension is stopped at once and films are made in the correct position to show the lesion, if an obstructing lesion or any questionable findings are observed. In the case of a lesion in the upper sigmoid colon, the flow of barium suspension may have been only started. Films are made in the left oblique position before barium has reached other loops of the colon or ileum, which may cover the suspicious area in the usual single film made after complete distention of the colon.

3. The film examination must include one or more films taken after the expulsion of the enema, as well as the one taken before expelling the enema. Although films made at both times are important, the one made after the enema is expelled is more important in the discovery of an early lesion. At this time there is the earliest evidence of a mucosal lesion because the mucosal markings are visualized. There is contracture of the longitudinal musculature as well as the circular musculature of the colon so that it is shorter. Many redundancies have disappeared. We routinely combine mucilage of acacia and tannic acid with our barium suspensions so that the mucosal markings are observed to best advantage in the films made after the expulsion of the enema.

4. Air or gas insufflation after the expulsion of the barium enema and the taking of stereoroentgenograms are done if the above procedures result in questionable findings or if there is clinical evidence of polyposis. This procedure is not necessary in most instances and is not done as a routine. Its use has resulted in the diagnosis of an early lesion when the other findings have been indeterminate.

CARCINOMA

The operative removal of early cancer of the rectum or colon is followed by better results than is the case of cancer in any other part of the digestive tube. Notwithstanding, by the time a diagnosis is made,

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approximately one-half the patients are found to have hopelessly inoperable lesions. In order to cure a larger number of these patients, earlier diagnoses must be made in the presence of less symptomatic evidence of cancer than has been the custom in the past.

The *symptoms* usually mentioned in the textbooks are *late* symptoms. We believe an unexplainable change in bowel habit is the most significant early symptom, but even this is not always present when the patient is first seen by the physician. Although most patients having this disease are in the usual carcinoma age, we are seeing an increasing number of patients between the ages of twenty-five and forty.

Patients having carcinoma of the rectum usually complain of passing rectal discharges, containing blood and mucus, if not pus. Any patient who has had a change in bowel habit and complains of unusual rectal discharges should have a digital and proctosigmoidoscopic examination without hesitation. Actual pain is a late symptom unless the anal canal is involved. If there is excessive loss of weight and strength, as well as pain, the lesion is usually extensive and metastases may be present.

Lesions in the right half of the colon produce different symptoms from those in the left half of the colon. When we think in terms of embryology and physiology, it is recalled that the right half develops from the mid-gut; it has a much larger lumen than the left colon; the lymphatics are more plentiful; its contents are liquid and rich in organisms of high virulence and its chief function is absorption. Therefore, obstructive symptoms are rare in cancer of the right colon unless the ileocecal valve is involved. Due to toxic absorption through the abnormal mucous membrane, some degree of cachexia and a marked secondary anemia are often present. By the time the patient consults a physician, a palpable mass may be present.

A physician, aged thirty-seven, came to us complaining of a severe secondary anemia for which he had been taking iron both by mouth and by vein for at least one year, without avail. He had a "gaseous dyspepsia" which he did not believe was significant and a roentgen examination of the colon had not been made. His hemoglobin was 39 per cent and a palpable mass was felt in the cecum which was shown by roentgen examination to be an extensive carcinoma. An inoperable carcinoma of the right colon with extensive metastases was found at operation.

In considering the symptoms of carcinoma in the *left half of the colon*, there is a contrast to those in the right colon. The left colon is derived from the hind gut, the lumen is much smaller than that of the right colon, the lymphatics are relatively sparse, its contents relatively solid, and its function is primarily storage, rather than absorption. Because of the smaller lumen, containing fecal material which is relatively solid, *obstructive symptoms* occur early in carcinoma of the left colon. Al-

though bright red blood may be observed in the stools, there is usually no anemia or cachexia and there may be no palpable mass.

The passage of bright blood by rectum may be the only symptom produced by a carcinoma of the sigmoid colon. This may be attributed to hemorrhoids.

To summarize the significant early symptoms of carcinoma of the colon, we have found that an unexplainable change in bowel habit in a person of cancer age is present in most instances, and is practically always present in lesions of the left colon. A severe secondary anemia may be the only evidence of a lesion in the right colon. Obstructive symptoms occur relatively early in lesions of the ileocecal valve and of the left colon. The roentgen examination is the most important diagnostic procedure in determining the presence of carcinoma of the colon above the reach of the proctosigmoidoscope.

BENIGN TUMORS

Benign tumors of the colon and rectum, in our experience, are relatively rare, and the ones we do see are usually adenomatous polypi. These must not be confused with the pseudo-polypi associated with ulcerative colitis. True polypi should be considered as precancerous lesions, regardless of whether or not they are familial.

There may be no symptoms, or there may be bleeding, prolapse or occasionally obstructive symptoms, due either to an encroachment upon the lumen or to intussusception.

We have found that adenomatous polypi are most common in the rectum, or if they are present elsewhere in the colon they are usually also found in the rectum. The proctoscopic examination generally gives the first clue to diagnosis. In these instances the roentgen examination should include an air or gas insufflation after the expulsion of the enema because, if polypi are present above the rectum, each may have a narrow pedicle at the mucosal junction which will result in very little disturbance of the general lumenal contour of the colon as visualized by the usual roentgen procedures.

The bleeding of an adenomatous polyp in the rectum may lead the clinician to believe that he is dealing with chronic ulcerative colitis, until the proctoscopic examination is made. The removal of a rectal polyp through a proctoscope is curative, of course, but proctoscopic examinations should continue to be made from time to time thereafter in order to make certain there is no recurrence.

DIVERTICULOSIS AND DIVERTICULITIS

In a series of 3000 consecutive roentgen examinations of colons, we found the incidence of diverticulosis to be 6.6 per cent. In most in-

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stances the diverticula were limited to the sigmoid colon but they may occur in any part of the colon.

There may be no symptoms attributable to the presence of the diverticula or there may be an associated colonic instability. As is well known, acute diverticulitis resembles a left-sided appendicitis, while in the chronic forms there is usually a history of recurring attacks over a comparatively long period of time. Urinary symptoms may predominate, due to extension of the process to the bladder wall. The most frequent complication of diverticulitis is obstruction, and this may lead to the belief that the obstruction is due to carcinoma. Other complications, such as acute perforation, abscess, fistula, and the association of malignancy with the diverticulitis, have been rare in our experience.

The diagnosis is made by roentgen examination, but it must be remembered that the diverticula may be visualized at one examination and not at another, depending upon the fecal content at the time of the examination.

Nonspecific Chronic Ulcerative Colitis

The incidence of this serious disease, which is most common between the ages of fifteen and forty, seems to be increasing. The most extensive involvement is usually in the rectum and the process becomes less extensive in a proximal direction of the colon. However, in seven per cent of our cases the process was localized in a limited segment of the colon.

As yet there is a lack of unanimity of opinion in regard to the cause of this disease. Bargen, who has reported more than 2000 cases, believes it is due to a diplostreptococcus. He attributes the decreasing number of ileostomies done at the Mayo Clinic for this condition to the use of sera and vaccines made from this organism. Some writers believe the disease is a form of bacillary dysentery and that the diplostreptococcus is one of the secondary invaders. Others are of the opinion that it is a manifestation of nutritional deficiency disease. Mackie reports relief of symptoms over a long period of time in 50 per cent of his cases when the condition is treated from the standpoint of gastro-intestinal allergy, and so on.

The diagnosis is usually made by proctoscopic examination which shows a spongy, granular mucosa which bleeds easily when touched with a cotton swab. There may be multiple miliary abscesses and ulcers. Smears from the rectal scrapings and culture are routinely made. The criteria established by Bargen and Buie need greater emphasis in the appraisal of this disease.

The proctoscopic findings may be those of a diffuse hemorrhagic proctitis with edema. The various stages of a diffuse inflammatory process are usually observed, the stage and severity of which depends on the time the patient is examined in relation to the course of his disease. The stool examinations give information relative to the quantity of blood and pus being expelled and permit additional studies of cultures.

The roentgen examination gives important evidence relative to the extent of the disease and is necessary in order to make a diagnosis of the segmental or localized form above the reach of the proctosigmoidoscope. However, in many cases where the disease is limited to the lower sigmoid colon and rectum the roentgen examination may show no abnormality.

In other words, normal roentgen findings do not exclude a diagnosis of chronic ulcerative colitis. On the other hand, roentgen findings pertaining to the left colon which may be interpreted as indicating the presence of this disease, may not be substantiated by the stool and proctosigmoidoscopic examinations. It is not uncommon for us to observe patients who have had a diagnosis of chronic ulcerative colitis, made from the roentgen examination alone, who later proved to have only an unusually spastic colon due to the self-use of irritating cathartics, enemas or colonic irrigations over a long period of time.

From the diagnostic standpoint we must realize that no diagnosis of this serious disease is established until all three of the examinations; stool, proctoscopic and roentgen examinations have been done. The outlook for the patient's future welfare demands this minimum examination.

In many cases the seriousness of the problem justifies the inclusion of a roentgen examination of the chest, a complete gastro-intestinal series, roentgen examination (including cholecystography) and special examinations of other parts of the body, which may reveal findings of etiologic significance if not findings of significance from the standpoint of general treatment of the individual. We have found that when the patient does not make satisfactory progress on treatment there may be a lack of thoroughness at the time of the initial examination.

AMEBIASIS

The diagnosis of amebiasis is usually made by finding the Endameba histolytica in the stools or by proctoscopic examination. About one-third of the patients who have active amebic dysentery have characteristic lesions in the rectum. The ulcers are larger than those seen in chronic nonspecific ulcerative colitis, have a punched-out appearance and the mucosa between the ulcers has a normal appearance. The organisms are found in the base of the ulcer.

When the proctoscopic examination is not diagnostic, formed stools are examined for cysts, and warm liquid stools obtained after the administration of Epsom salts are examined for motile forms. In our experience, the roentgen examination results in negative findings. This is important in the exclusion of other disease.

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In the absence of evidence of amebiasis in the stool and proctoscopic examinations, the clinician may still believe that there is amebic infection in the wall of the intestine or elsewhere in the body. Under these circumstances in a therapeutic test for amebiasis, the use of emetine usually brings the acute attack under control quickly, but it alone will not effect a cure. Emetine must be used with care because of its toxic effect on the myocardium and it may produce a peripheral neuritis. Since it affects primarily the organisms in the tissues of the bowel, the use of oral medication such as carbarsone and vioform have been used to affect the organisms in the lumen of the bowel. As in cases of peptic ulcer, chronic ulcerative colitis, and other gastro-intestinal diseases, we believe the most important feature in the treatment of amebiasis is continued supervision of the patient's management over a period of time. Stool examinations, made every three to six months should remain negative for eighteen months before one can assure the patient of cure.

TUBERCULOSIS OF THE INTESTINE

Roentgen evidence of ulcerative involvement of the terminal ileum and cecum, the site of predilection, in a young adult who has pulmonary tuberculosis or a primary focus elsewhere in the body, makes the diagnosis of intestinal tuberculosis highly probable. However, many patients with this disease do not have symptoms or signs of pulmonary tuberculosis at the time the physician is consulted. Therefore, whenever an ulcerative condition is found in the terminal ileum or cecum, a roentgen examination of the chest is indicated, even though physical examination shows no evidence of pulmonary involvement.

The hyperplastic form often presents roentgen evidence in the cecum which is difficult, if not impossible, to differentiate from a neoplasm. Tuberculoma usually occurs in young individuals, and its duration is usually in terms of years. The surgical treatment is the same in both lesions. In the ulcerative form of tuberculosis, surgery is usually contraindicated unless the primary focus is inactive or complications are present.

REGIONAL ENTERITIS

Although this entity which was established by Crohn, Ginsburg, and Oppenheimer in 1932, as "Regional Ileitis," is most commonly related to the terminal ileum, it may be found in any part of the small intestine and there may be associated lesions in the adjacent colon. Crohn has reported sixty cases, in nine of which there were associated lesions in the colon. The pathologic changes are those of a low grade, chronic, cicatrizing process with a tendency to formation of fistulas.

The symptoms, of course, vary with the stage of the disease at the time the patient is seen. Early in the course of the disease, the symptoms simulate those of recurring appendicitis even though the appendix has been removed. The patient usually consults the physician during the ulcerating enteritis phase when the symptoms are similar to those of chronic ulcerative colitis, that is, diarrhea with pus and blood in the stools. Later, during the stenotic phase, the signs are those of partial obstruction. Fistulas may form at any stage.

Roentgen examination helps in the differentiation from ulcerative colitis. When the disease is limited to the small intestine, the barium enema will give evidence of a normal colon, which in view of the symptoms which suggest colonic disease, is important negative evidence. If the lesion is limited to the terminal ileum, its most frequent site, the regurgitation of the barium enema through the ileocecal valve discloses evidences of ulceration which is positive evidence. If the stage and extent of the disease is not clearly established by this examination, interval roentgen studies of the small intestine must be made after the administration of a barium meal. Tuberculosis is considered to be eliminated in most instances if the roentgen examination of the chest gives negative findings.

MEGACOLON

The diagnosis of megacolon is easily established by roentgen examination, using the barium enema. The use of a spinal anesthetic has proved helpful in two respects—it gives relief for several months in some cases, and it furnishes a means of determining the likelihood of cure by doing a lumbar sympathectomy. The use of pitressin and acetylcholine has proved significant in the appraisal of this condition.

BENIGN STRICTURE OF THE INTESTINE

Benign stricture of the intestine due to irradiation of carcinoma of the cervix uteri has been found in fifteen of 800 cases, an incidence of 1.9 per cent. Although this apparently is a rare condition, its presence should be suspected when a patient gives a history suggesting partial or complete intestinal obstruction subsequent to the original radiation therapy, particularly if pelvic examination reveals normal findings. The condition may be encountered months or even years after irradiation and its incidence, where metastatic lesions from a carcinoma of the uterine cervix are suspected, may be greater than has heretofore been recognized. In our cases, the most common location of the stricture was in a redundant sigmoid colon and the diagnosis was made by the roentgen examination, using the barium enema. At operation, there was no evidence of carcinoma in any of our cases. Resection of the involved segment and end-to-end anastomosis is curative.

DIAGNOSIS AND TREATMENT OF CARDIOSPASM

PAUL M. MOORE, JR., M.D.

The condition known as cardiospasm has been attributed to many causes and many names have been offered by the proponents of the various theories to take its place. But the name cardiospasm has remained the one that has been the most frequently used, partially because the various theories advanced were not altogether convincing, and partially because the names suggested were too cumbersome. The most recent term, achalasia of the cardia, sponsored by Arthur F. Hurst¹ is being used more and more in the English literature and is appearing more frequently now in America. The term is short and easily used and the theory behind it has considerable merit.

The earliest case was reported by Thomas Willis² in Pharmaceutice rationalis in 1672. He made a dilator of whalebone surmounted by a button of sponge which the patient used on himself for fifteen years. The early literature classifies these cases as Idiopathic Dilatation of the Esophagus.

An excellent and complete review of the literature has been made by Sturtevant³ and the earlier theories have been well covered by Freeman⁴ so I will make only brief reference to some of the better known theories.

Cardiospasm. This is one of the earliest theories and has been the most popular. It was sponsored by Kraus, Meltzer and Mikulicz. It would account for the obstruction to the passage of food into the stomach and for the beneficial effects of belladonna and atropine. It does not explain the marked dilation of the esophagus in the later stages. Such dilation is not seen in obstruction due to other causes, such as scar tissue stenosis, even after it has been present many years. Opponents of this theory point out that there is no definite anatomic sphincter muscle at the cardia. Recently, Lendrum⁵ came to this conclusion after studying 150 human specimens. On the other hand, Knight⁶ has demonstrated a physiologic intrinsic sphincter at the cardia in cats which contracts on sympathetic stimulation and relaxes on vagal stimulation.

Phrenospasm. This has been advanced by Jackson⁷ who tries to explain the condition on the basis of a spasm of the diaphragm which acts as a pinch cock on the lower end of the esophagus. Although he has supplied an anatomic sphincter in this theory, it still does not explain the marked dilatation of the esophagus in later cases. Then, too, the obstruction to the passage of food is sometimes below the diaphragm.

Fibrosis of the terminal portion of the esophagus. This is the most recent theory of Mosher⁸. He feels that there is a tubular narrowing of the terminal portion of the esophagus in the crural canal and crural ring due to a fibrosis of the periesophageal connective tissue and of the

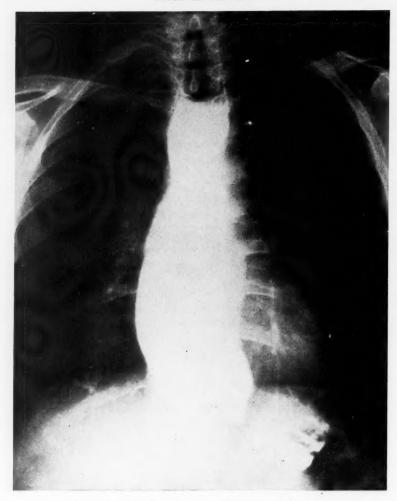


FIGURE 1. Typical roentgenogram illustrating cardiospasm.

muscles of the esophagus. He believes this is brought about by infection of the coats of the esophagus. The fibrosis of Auerbach's plexus reported by Hurst¹, Rake⁹ and others is interpreted as being of secondary rather than primary importance. He reports three cases which he has studied from the standpoint of involvement of the plexus. One case of five years' duration showed no involvement of the plexus. One long-standing case showed some involvement and a man of seventy showed marked involvement of the plexus.

Achalasia of the cardia. This term was introduced by Hurst⁹ in 1915 and has been gaining in popularity ever since. He and Rake are the principal champions of the theory that the condition is due to a failure of the cardia to relax and open during the act of swallowing rather than due to a spasm. They found that this theory had first been suggested by Einhorn¹⁰ in 1888 and again by Rolleston¹¹ in 1896. According to this theory, the cardia is normally closed when at rest and opens as a result of a peristaltic wave passing down the esophagus. Normally a bolus of food is swallowed, the peristaltic wave passes down the esophagus to the cardia where there is a momentary pause, then the cardia opens and the bolus passes into the stomach. In achalasia, the cardia fails to relax and the food remains in the esophagus. This, they feel, is due to a neuromuscular dysfunction resulting from pathologic changes in the vagi and more particularly in Auerbach's plexus. Hurst, Rake and more recently Lendrum⁵ have reported numerous cases in whom careful postmortem examination has revealed a striking loss or complete absence of the ganglion cells in the myenteric (Auerbach's) plexus. Freeman⁴ and Mosher⁸ report one case each that showed no involvement of this The clinical and roentgen picture has been produced in rabbits 12 and in cats 6 by section of the vagus nerves. Symptomatic relief was produced by subsequently sectioning the sympathetic. On the basis of these experimental investigations, a number of reports have been made of resection of the sympathetic supply to the cardiac sphincter in the treatment of this condition 12, 13.

That there are psychogenic features in most cases of cardiospasm cannot be denied, but whether they are of etiologic significance or are byproducts of the condition is another question. Winkelstein¹⁴ feels that a certain number of cases are on a psychogenic basis and can be helped by psychotherapy. Most of these cases are extremely nervous, and sudden nervous tension or strain does make them worse but it seems to me that the condition itself is enough to produce nervousness. The psychogenic factor could hardly enter into the cases which have been reported as occurring in the newborn by Segar and Stoeffler¹⁵, Aikman¹⁶, and Bogert¹⁷.

Although cardiospasm is most frequently found in young adulthood, it has been reported as occurring from the first day of life to old age. The symptomatology varies with the severity of the condition and the length of time it has existed. In the newborn it may cause vomiting during or immediately after the first feeding. There is no gastric juice in the vomitus. A barium esophagram shows the typical picture of obstruction at the cardia with dilation of the esophagus above.

Usually the patient with cardiospasm does not consult the physician for some years after its onset. At first there is the sensation of food

sticking momentarily in the lower end of the esophagus. This is intermittent at first. As the condition becomes more established and more frequent, there often develops a pain or feeling of pressure which is substernal or in the epigastrium. This pain is increased by taking food and may become very severe and may radiate through to the back. Regurgitation is a very common symptom and the regurgitated food has an alkaline reaction and may show some putrifaction but no digestion. As the esophagus becomes more and more dilated, a shortness of breath develops on exertion or on lying down. The closed cardia will support a column of water eight inches high and as much as 2000 cc. of fluid content has been aspirated from one dilated esophagus. As a result, the patient has much difficulty resting at night both because of the pressure of the overloaded esophagus and because the liquid contents often leak out and spill into the larynx, bringing on severe paroxysms of nocturnal coughing. Most of the patients discover that they can attain some small degree of comfort by voluntarily regurgitating as much as possible. They also find that in the earlier stages they can aid the passage of food into the stomach by taking a sip of hot water or sometimes by taking a deep breath or twisting the body one way or another. Because of the esophageal irritation, there may be increased salivation which may be very annoying to the patient. In extreme longstanding cases there is loss of weight and strength, and anemia.

The diagnosis is made by esophagram and esophagoscopy. The roentgen picture is typical but esophagoscopy should always be done, for the cardiospasm may be secondary to a peptic ulcer of the esophagus or an early malignancy. On esophagoscopy, the dilated esophagus is always partly filled with a frothy liquid content which may contain partly decayed bits of food. The mucosa is a gray or mottled red and may be ulcerated. There is always an esophagitis. Carcinoma has been known to develop²⁰. The Jackson dilators meet with only a little resistance as they are passed into the stomach.

The treatment must consist of a definite program which the patient must adhere to in order to obtain the best results. Every one of these cases can be very definitely helped. Complete permanent cure is questionable. In the newborn the passage of a small catheter through the nose and esophagus into the stomach where it is allowed to remain for one or two days for feedings is usually enough. This may be repeated if necessary.

The patient is put on a diet of bland liquids and soft food. He is warned against eating any highly seasoned food and especially against foods with seeds or pits that would be irritating. As his condition improves he can add more solid foods to his list.

In spite of the frequency with which the published papers insist that

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antispasmodics are disappointing, I still prescribe them. I use them because I have seen patients make better progress when they were used than when they were left out of the plan. They can be given as tincture belladonna, XV drops, t.i.d.a.c.

A mild sedative is also very desirable. I give phenobarbital gr. ½ t.i.d.a.c. One can combine the antispasmodic and sedative in the following prescription:

Sod. Bromide	3 IV
Tr. belladonna	3 IV
Tr. hyoscyanus	3 IV
Simple elixir q.s. ad.	3 IV

Sig.; 1 tsp. t.i.d. one hour before meals.

In addition to the above measures the cardia is dilated mechanically at intervals, depending on the severity and the reaction of the patient. I like to give a dilation about once a week and then lengthen the intervals as the patient improves. Many dilators have been designed and are in use today. I prefer the mercury filled bougies and start with the num-This is done one-half hour after giving the patient 1½ gr. nembutal and anesthetizing the throat with a spray of 2 per cent cocaine. If the patient tolerates the procedure well, I pass the next size, the number 30. Each dilator is left in place about five minutes if possible. As the patient becomes more used to the procedure, two can be passed each time. When the largest size, the number 34 is reached, I like to have them swallow the Mosher bag and pump it up to four pounds for five minutes. This produces a larger amount of stretching than is possible with the nonexpanding type of dilator but it is extremely difficult for some people to The periods between dilations can be lengthened from time After the largest dilation is reached, the patient is instructed to return when he feels the need of another dilation.

Bruenner¹⁸ advocates treatment with the high frequency current in conjunction with the dilation. She uses the dilator as one electrode and the other electrode is attached to one disc on the front and one disc on the back of the patient.

Very severe cases with marked esophagitis may run a septic temperature following any manipulation. These should be handled as advised by Canfield¹⁹. He does a gastrostomy and then irrigates the esophagus with 1,000 cc. hot physiologic saline solution one to three times a day. Temporary gastrostomy is at times very helpful in controlling a far advanced case. Many other operative procedures have been done but it is not within the scope of this paper to discuss them. Thus far it would seem that they apply to only a very few of these cases unless the recently devised sympathectomy proves to give a permanent cure.

PAUL M. MOORE

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THE CHEMOTHERAPY OF PNEUMONIA

R. H. McDonald, M.D.

The introduction of sulfanilamide as a therapeutic agent caused a tremendous increase in interest in the subject of chemotherapy generally and following the demonstration of its success against the hemolytic streptococcus, it was tried extensively in pneumococcal infections. A considerable degree of therapeutic success was obtained but its value was somewhat lessened by the severe toxic effect. Efforts were then made to produce related compounds of lessened toxicity. In May, 1938, Whitby¹ published his results in protection of mice from experimental pneumococcal infections with a new compound first labeled M & B 693 or dagenan, which has come to be known in this country as sulfapyridine. Chemically it is 2- (P-aminobenzenesulphonamido) pyridine. Whitby demonstrated that this compound was of low toxicity and would protect mice against 10,000 lethal doses of Type I pneumococcus and that it would afford a high degree of protection against infection with Types II, III, V, and VIII pneumococci.

Evans and Gaisford² reported the results of a study of 100 cases of pneumococcal pneumonia treated with this compound in July, 1938. They recorded a mortality rate of 8 per cent in a group of cases treated with this material as against 27 per cent in a control group of 100 cases receiving nonspecific treatment. This remarkable advance in the therapy of a difficult infection attracted widespread attention and has now been confirmed by numerous investigators^{3, 4, 5} whose reports show that the average mortality figures have been reduced from the usual 25 to 30 per cent to figures ranging from 3 to 11 per cent.

The present report is an attempt to evaluate the success of sulfanilamide and sulfapyridine therapy at the Cleveland Clinic since the introduction of each of the drugs in all pneumonias, whether of the lobar or bronchopneumonic type. Sulfanilamide was used in these cases from the time it became available until the early months of 1939 when sulfapyridine was introduced. There were altogether forty cases, with a diagnosis in twenty-seven of bronchopneumonia, and in thirteen of lobar pneumonia. Of the bronchopneumonia, it was considered that only six represented an uncomplicated, pulmonary infection, the others being patients with severe, pre-existing disease. In the majority of this latter group, it is apparent that conditions apart from the lung form the primary difficulty, the pneumonia being in many instances purely terminal. some of these complicated bronchopneumonia cases, death was inevitable from other conditions, but for the sake of completeness, they have been included in this study. Of fourteen cases of bronchopneumonia treated with sulfanilamide, there were three recoveries and eleven deaths. Of these cases, only two were considered to be uncomplicated broncho-

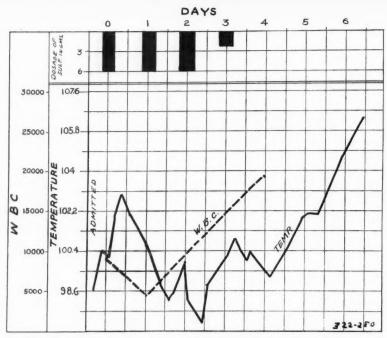


FIGURE 1: Graphic chart of Case 1. Sulfapyridine levels were not obtained.

pneumonia and both recovered. There were thirteen bronchopneumonias treated by sulfapyridine, with seven recoveries and six deaths. Of this group, four were considered to be uncomplicated cases of bronchopneumonia and all recovered. In the lobar pneumonia group, there was one case treated with sulfanilamide with recovery and twelve cases treated with sulfapyridine with ten recoveries.

Sputum examinations in the bronchopneumonia group showed a variety of organisms with the streptococcus predominating, whereas the pneumococcal group showed Types III, VI, VIII, XIV and XIX. Types I and II were not represented and the type was not determined in four cases.

The dosage of sulfanilamide used varied considerably with the clinical findings. On the average, approximately 20 grains was given every four hours, day and night, during the first two days, with a reduction thereafter of the dosage to 15 or 10 grains every four hours, depending upon the blood concentration, the level being checked each morning. A therapeutic level of between 10 and 15 mg. per 100 cc. was regarded as being of maximum therapeutic efficiency, and the dosage was varied in individual instances to secure this level. In the cases treated with sulfapyridine, the usual initial dosage was 2 grams followed by 1 gram every four hours day and night. Daily blood estimations were made in an

THE CHEMOTHERAPY OF PNEUMONIA

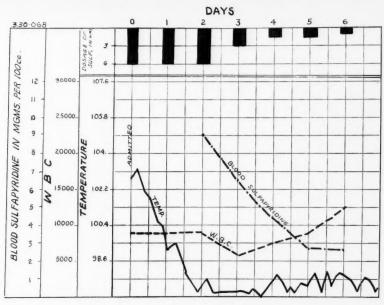


FIGURE 2: Graphic chart of Case 3.

attempt to maintain the level at between 5 and 10 mg. per 100 cc. Therapy was maintained at this level when possible, for at least two days after the patient was temperature-free; then the dosage was reduced gradually. The total dosage varied between a lower limit of 20 grams to an upper Sodium sulfapyridine monohydrate limit of 66 grams in one instance. was not used in this series. It was very evident that the concentration of the drug in the blood stream varied greatly in different patients on the same dosage. Particularly in the patient with renal failure it was found that the concentration of the drug tends to increase rapidly, whereas in other instances, even with large doses of the drug, it was impossible to raise the blood level to the desired limit, apparently due to a failure of Thus, in one instance of Type XIX pneumococcal pneuabsorption. monia, a blood sulfapyridine level of 4.5 mg. per 100 cc. was the maximum attained on the above medication and rapidly fell off when the dosage was reduced in accordance with clinical improvement to levels of 1.8 mg. and 1.2 mg. per 100 cc. In another instance on the above mentioned dosage, the blood level reached 9 mg. on the morning of the second day and was maintained at a level averaging 6 mg. per 100 cc., even with reduction of the oral dosage. This patient had a heavy albuminuria on his admission which cleared up within three days of his hospital entrance.

It is difficult to see that the effects of sulfanilamide or sulfapyridine

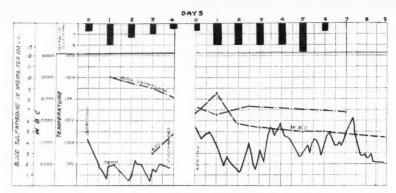


FIGURE 3: Graphic chart of Case 4.

have affected the clinical course of the complicated bronchopneumonia group. As stated above, it is our opinion that the bronchopneumonia was merely an expression of their terminal condition. In those complicated bronchopneumonias with extra pulmonary conditions not necessarily immediately fatal, it was our clinical impression that the effects of the drug were distinctly beneficial. In the uncomplicated bronchopneumonias, a rapid reduction of temperature was accomplished with both sulfanilamide and sulfapyridine, the effect being somewhat more striking with the latter. The reduction of temperature to normal and its maintenance at a normal level was not as striking, however, in this group as was the result in the lobar pneumonias—to be discussed later. Frequently some recurrence of temperature was noted, suggesting some flare-up of the lesion, but in general the results of therapy have been reassuring and suggest that in the various bronchopneumonias of indeterminate origin, a trial of this therapy is indicated.

In regard to the lobar pneumonia, the striking finding has been a rapid reduction in temperature, usually to normal, within a period of twenty-four to thirty-six hours. This has been such a constant feature that its nonappearance suggests either inadequate therapy or the presence of a pneumonia of other than pneumococcal origin. In several instances the temperature has remained normal from that time on, whereas at times there have been slight recurrences of fever within the next few days. In some instances this has been due to insufficient dosage with an increase in the pulmonary lesion. In a few instances it has been caused by a specific drug fever. It may at times be difficult to distinguish between the two causes. An increasing temperature after three or four days of treatment in the face of apparently adequate therapy suggests the possibility of drug fever. A decreasing white blood count even to the point of leukopenia also suggests the drug basis for fever whereas an increasing leukocytosis is suggestive of a spread of the pulmonary lesion. Withdrawal

of the drug causes cessation of the specific drug fever within a few hours. It is interesting to note that despite the increase in well-being felt by the patient, and the favorable temperature chart, the pulmonary process apparently goes through its normal stages of congestion and hepatization with final resolution in the usual fashion, although it would appear that these processes are somewhat accelerated. In general it would appear that a beneficial effect can be readily noted within a three-day period, if it is going to occur.

Symptomatically, the effect of sulfapyridine therapy may be very striking. Headache, malaise and restlessness which are commonly seen at the beginning of treatment tend to subside within the first two days and may be replaced by the lassitude which is commonly seen when the drug is administered. There would appear to be some slowing up of mental processes and the apprehension frequently seen in these patients is distinctly lessened. With the reduction in fever, the fluid loss in perspiration is greatly reduced and the necessity for the administration of large

quantities of fluids becomes lessened.

The incidence of toxic manifestations with both sulfanilamide and sulfapyridine therapy has been relatively small. With both drugs most of the patients experience nausea within a few hours and in about onethird of the cases actual vomiting occurs. This is somewhat more likely to occur with sulfanilamide than with sulfapyridine and, particularly with sulfanilamide, nausea may be decreased by the use of equal amounts of sodium bicarbonate. It has been amply demonstrated that the nausea and vomiting of themselves do not constitute an indication for stopping the drug, since persistent use of the drug may result in marked lessening or disappearance of this symptom. Dosage lost in this way should be replaced immediately. It was found that crushing the tablet will frequently tend to reduce this effect, and dissolving the medication in orange juice or milk or dividing it into small doses every hour may be effectual. Occasionally the vomiting may be reduced by the use of simple sedatives, and in a few cases we found it necessary to administer glucose and saline intravenously to combat fluid Cyanosis is present in practically all patients to some degree although it is somewhat questionable what part of this is due to the drug itself in a disease characterized frequently by cyanosis. A drug eruption was noted in two patients and definite drug fever appeared in one patient. A few red blood cells were noted in the urine in three cases, but gross hematuria and ureteral colic were lacking in our series. A mild hypochromic anemia developed in three patients; granulocytopenia was not seen in any case.

The essential findings in the two fatal cases were as follows:

Case 1: A sixty-four year old man was admitted with pneumonia of the right lower lobe. Type XIV pneumococcus was demonstrated in the sputum. Other laboratory findings showed a two plus albuminuria, a blood urea of 111 mg.

per 100 cc. and a white blood cell count of 9,600 with 98 per cent neutrophils. On routine sulfapyridine therapy there was an initial decrease in temperature to normal for one day, then the temperature began to rise again and continued upward despite sulfapyridine therapy. The white blood cell count rose to 18,000 and the blood urea rose to 144 mg. per 100 cc., despite adequate fluids. The patient died six days after treatment was started, with renal failure probably playing a large part in this outcome.

Case 2: A seventy-two year old man was admitted with evidence of pneumonia involving the lower two-thirds of the left lung. There was some question of involvement of the right base. Type VI pneumococcus was isolated from the sputum and 100,000 units of Type VI antipneumococcus serum was given with 8 grams of sulfapyridine in the first twenty-four hours. Subsequent sputum examination revealed the presence of a Type III pneumococcus and another 100,000 units of serum was given. The blood culture was negative. The white blood cell count was reported as 5,950; it gradually rose to 12,000 but then dropped back to 6,000. Abdominal distention became very marked and the patient expired, apparently of cardiac failure. This patient had suffered from chronic malnutrition for several months prior to his pneumonia from a large esophageal diverticulum.

An ideal result is shown in the following case history:

Case 3: This forty-eight year old man was admitted to the hospital one week after the onset of a cold with some chilly sensations. Physical examination at the time of admission showed only a slight pleural rub in the left chest anteriorly but roentgenogram of the chest showed an extensive infiltration in the left upper lobe, apparently a lobar pneumonia of the upper left lung. The blood culture was sterile. The white blood cell count was 8,800; urine on admission showed heavy albuminuria with a moderate number of hyaline casts and a few white blood cells. The icteric index was 20. On sulfapyridine therapy the temperature decreased from the admission temperature of 103° F. to normal in thirty-six hours, and remained constantly below normal from then on. Physical signs in the chest remained minimal at all times but it was five days after his admission before the X-ray showed evidences of resolution of the pneumonic process.

An example of relapse of the infection following too early discontinuation of the drug and of probable drug fever on too prolonged administration during the second course is seen in the following case history:

Case 4: This was a seventy-eight year old man who had experienced a previous attack of lobar pneumonia of the right lower lobe in April, 1939, which had been treated with sulfapyridine with an excellent response. He was admitted to the hospital on December 27, 1939, with evidence of pneumonia of the right lower lobe. Temperature on admission was 100.5° F., white blood cell count was 13,700 and the pulse rate was 96. On sulfapyridine therapy the temperature dropped to normal within a period of twelve hours and remained there. After four days of perfectly normal temperature, the patient pleaded to be allowed to go home by ambulance and therapy was discontinued. Three days later he was readmitted with evidence of a recurrence of his infection, temperature 101.3° F., pulse 96. Sulfapyridine therapy was again started and within thirty-six hours the temperature reached the normal line. Shortly thereafterwards it increased and continued at an average of approximately 100 to 100.5° F. On the sixth hospital day the sulfapyridine was discontinued and, although the temperature reached 102.5 the following day, it subsequently declined and reached normal thirty-six hours later. The white blood cell count, which had been 21,000 on the

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second admission had meanwhile declined and at the height of the hyperpyrexia was only 13,000.

SUMMARY

In accordance with the general conception, it is our opinion that the introduction of this specific chemotherapy has vastly increased our therapeutic armamentarium against both lobar and bronchopneumonias. In streptococcal bronchopneumonia and especially a lobar pneumonia sulfapyridine has given dramatic results. Although in this small series of lobar pneumonias treated with sulfapyridine the mortality rate of 16 per cent is more than in many reported series, careful analysis of the fatal cases indicates the presence of extrapulmonary factors which were the main cause of failure.

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THE NEUROSURGICAL MANAGEMENT OF INTRACTABLE PAIN

W. JAMES GARDNER, M.D. and WM. A. NOSIK, M.D.

The management of intractable pain can represent a sore trial for the patient and the physician alike. To the patient presenting himself with this common symptom, it is usually the most significant phase of his ailment and the one from which he desires most to be relieved, regardless of its cause. To make a diagnosis and to make the patient comfortable while directing attention to the elimination or amelioration of the cause of the pain should be almost axiomatic with the physician. Hypnotics and analgesics have been used with varying degrees of relief in the individual case. Employed often in near-lethal doses to accomplish the desired effect, the penalties of prolonged usage often outweigh the benefit of their administration. Hence the application of neurosurgical measures in certain cases affords a more satisfactory solution, both from the standpoint of the patient and of the physician. Interruption of the pain conduction pathways forms the usual basis of this type of treatment.

The neurosurgical management of headache due to encroachment upon the cranial cavity by mass lesions such as tumor, abscess, subdural and extradural hematomas or hydroma resolves itself largely into a problem of removing the offending agent when possible, or resorting to decompression measures when their removal is impossible. This form of pain is due to the disturbed intracranial fluid dynamics and relief is obtained by re-establishing as relatively normal fluid relations within the skull as is possible. Of somewhat different mien is the post-traumatic or postinflammatory headache, when often no alteration of intracranial pressures exists. The use of encephalography or the direct insufflation of the subdural space on the affected side with air often affords relief to this particular group of patients as well as being of diagnostic value. In some severe unilateral post-traumatic headaches, relief can be afforded by interruption of the nerve supplying the painful zone. This nerve may be the supra-orbital, the greater occipital or the nervus spinosus, which accompanies the middle meningeal artery.

The pain of trigeminal neuralgia or tic douloureux is so well known that it hardly needs discussion. The afflicted patient will, in most cases, gladly exchange this excruciating pain for the anesthesia of the involved area which gives the much desired relief. The more temporary method of treatment is the alcohol injection of the various divisions of that nerve or their peripheral excision.

Recurrence of this pain usually follows these procedures in periods varying from several months to two years. With frequent repetition of the injections, the attendant fibrosis decreases the effectiveness of each injection until this method is no longer of any service. Permanent relief of pain is always experienced by those patients submitting to the total or the subtotal section of the posterior root of this nerve. The danger of a facial paresis is minimal and the numbness is permanent in the areas supplied by the sectioned nerve.

Atypical facial neuralgia should be carefully differentiated from trigeminal neuralgia in the consideration of facial pain, and in the use of surgical methods for its relief. Alcohol injections and section of the fifth cranial nerve are of no benefit in these cases.

Another painful affliction, resembling in its severity tic douloureux, is the more recently described glossopharyngeal neuralgia. Possessed often of a trigger point much like that of the true tic, and giving rise to an agonizingly severe, usually unilateral pain in the pharynx, larynx, eustachian tube or inner ear, this condition is every bit as distressing to the patient as is trigeminal neuralgia. Complete relief without any motor impairment of the laryngeal or pharyngeal musculature is obtained by intracranial section of the ninth cranial nerve through the unilateral approach.

Intractable pain due to a compressing or irritative lesion affecting either the spinal cord or its roots is a condition which requires laminectomy. Careful diagnostic approach to the problem will usually differentiate between a true neoplasm, herniation of the intervertebral disc, hypertrophied ligamentum flavum and other conditions less suitable to removal with amelioration of pain. In the event an inoperable lesion is found, decompression and section of the posterior nerve roots to the involved area afford the patient relief from pain.

Similarly, rhizotomy or intradural section of the posterior nerve roots as they leave the spinal cord has been a valuable aid in the treatment of tabes dorsalis, post-herpetic neuralgias and certain pain syndromes associated with visceral disease. In these conditions the response is not uniformly satisfactory, as neither the origin of the pain nor its mode of production is known.

Pain in an arm due to compression of the nerves or blood vessels by a cervical rib, a fibrous band, or a spastic hypertrophied anterior scalenus muscle is very satisfactorily treated by removal of the offending pressure agent or by division of the fibrous band or muscle.

As the knowledge concerning the parasympathetic and the sympathetic nervous system increases, more weapons are added to the neurosurgical armamentarium. Relief from the excruciating pain of angina pectoris is sometimes obtainable by the alcohol injection of the upper four thoracic ganglia of the left side. Laminectomy with excision of the middle, inferior cervical and first thoracic ganglia in the left has also resulted in freedom from pain. Section of the superior cardiac nerve

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has been effective in the relief of anginal pain, as has been the posterior rhizotomy. In severe primary dysmenorrhea, presacral neurectomy has been performed many times and has been uniformly successful when more conservative methods of treatment failed. This operation has also been successfully used in patients suffering from intractable pain due to inoperable carcinoma of the cervix and the uterus. Similarly, presacral neurectomy may be used to relieve the pain of a longstanding cystitis. However, in cases of malignancy of the bladder, it has been found necessary to remove both the sympathetic and parasympathetic innervations at the cost of a "cord bladder" to gain complete relief, although possibly cordotomy would be the operation of choice here.

Pain having its origin in the abdominal viscera may often be relieved by paravertebral alcohol injections by noting first the level of skin anesthesia at which pain disappears when a high spinal anesthetic is used and then using that dermatome level as an indication of the injection level. This treatment is effective for such lesions as carcinoma of the esophagus and upper gastro-intestinal tract, including the pancreas.

Neurosurgical methods are often the sole hope for the pain-wracked sufferer from an advanced malignancy of the lower sections of the body. Careful subarachnoidal injections of alcohol, done in such a fashion as to strive for its selective effect upon sensory nerves or their fibers supplying the involved area, frequently give marked relief from pain. Potential harm to the nerves supplying the bladder and rectum must be weighed against the relief of pain to be gained, together with the stage of the malignancy and the life expectancy. Cordotomy is an operation used all too seldom for the relief of pain of inoperable cancer. In this procedure an incision is made into the cord itself in such a position that the spinothalamic tracts are interrupted. Using this operation, relief of intractable pain is possible without impairment of motor function and it certainly makes the last days of these unfortunates pain-free and enjoyable to a degree hitherto not attainable by other measures.

THE ROLE OF ROENTGEN THERAPY IN THE TREATMENT OF BRONCHIOGENIC CARCINOMA

U. V. PORTMANN, M.D.

Bronchiogenic carcinomas are being treated by surgery, radium, roentgen therapy, and combinations of these procedures.

Attempts have been made to implant radon seeds or radium needles interstitially or to place other types of radium containers in apposition with the malignant tissue through bronchoscopes. Although apparently most carcinomas of the lung begin in major bronchi and near the hilum, radium treatment can be employed only in a few selected cases where the disease is so located that it is accessible through bronchoscopes or by some other equally simple surgical approach which facilitates the application of the radium containers. However, the sphere of therapeutic effectiveness of the radium radiation is only a few centimeters from its source; therefore, radium therapy has quite limited usefulness because in the majority of cases the carcinoma will have extended beyond its destructive influences. Also, it would seem that surgical excision would give better prospect of cure in the same types of localized growths for which radium treatment might be considered because of the accessibility of the tumor.

Undoubtedly, more patients with bronchiogenic carcinomas have been treated by roentgen therapy than by any other procedure. During the past ten years, a diagnosis of primary cancer of the lung has been made in sixty-three cases at the Cleveland Clinic. Of these, we have given roentgen therapy to thirty, most of the others having been too far advanced to justify treatment. Many of the patients were benefited; cough, pain, and hemoptysis were diminished but I cannot state that survival in any proved case was longer as a result of the treatment than the average life expectancy of about one year from the time the diagnosis was made.

The benefits and limitations of roentgen therapy for bronchiogenic carcinoma must be interpreted on the basis of our knowledge about the origin, development, and clinical course of the disease and also according to the physical and biological effects of the radiation.

Pathologists disagree about the classification of cancers of the lung on the basis of histogenesis and morphology. However, their controversies do not concern clinicians. It is certain that all bronchiogenic carcinomas originate in or from epithelial cells of the mucosa lining the bronchial system. Very few of these cancers are of pure unicellular morphology. They are pliomorphic. The degree of differentiation varies considerably in different growths and also in different areas of a single growth whether the predominate cellular structure is the squamous cell type with flattened cuboidal or cylindrical epithelial cells having

different shapes of nuclei and variations in stroma, or has the glandular arrangement of adenocarcinoma.

We know that the embryonic, less differentiated types of cells are the most radiosensitive while those of higher degree of differentiation are comparatively resistant. Epitheliomas, as a class, are well differentiated and therefore most of them are resistant. Since cancers of the lung are epitheliomas, they likewise are radioresistant even though some may be composed of a considerable proportion of comparatively undifferentiated types of neoplastic epithelial cells. Therefore, we cannot expect cancers of the lung or their metastases to be destroyed by any less intensity of irradiation than similar epitheliomatous neoplasms in other locations. It has been found that most squamous cell carcinomas or adenocarcinomas cannot be destroyed completely with an intensity of homogeneous radiation less than the equivalent of from 5,000 to 10,000 roentgens or Cancers of the lung which have similar origin, structure and growth characteristics must require as much as this to eliminate them. We cannot administer such great intensities into the chest safely by any technic now in use although we more nearly approach it by prolonged We probably do not administer quite as much radiation irradiation. into cancers of the lung as we estimate. It has been shown that the aerated lung is not nearly as good a scattering medium as solid structures. The secondary radiation may be nearly the same in the consolidated area of the cancer as in other dense tissues, yet that from the surrounding aerated lung is less; consequently, the total dose in the disease area is reduced to some extent and not as great as may be calculated from standard absorption charts.

In addition to the technical difficulties which confront roentgen therapists in destroying primary cancers of the lung, they have the same biological problems to deal with as surgeons. By the time the diagnosis of the disease is made, the mediastinal structures, including the lymph glands, usually are involved or metastases have developed in distant regions in the majority of cases. It has been proved that when carcinomas have metastasized to lymph nodes, the intensity of radiation that may destroy the primary growth completely may not be sufficient to eliminate the disease from lymph glands, although neoplastic cells in them may subsequently lie dormant for some time. Therefore, since cancers of the lung are almost always inherently radioresistant epithelial neoplasms that have usually metastasized to lymph glands before treatment is instituted, and since these metastases are equally resistant or more resistant than the primary growth, we cannot be optimistic about the possibility of curing the disease by methods of administering roentgen therapy that are in use today.

Unfortunately, some clinicians, especially surgeons, are prone to estimate the benefits of therapeutic procedures for malignant diseases only

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from statistical proof that the percentage of survivals for a specified time is increased in comparison with other methods. They often consider as ineffectual or useless those methods, the benefits of which cannot be computed on some arithmetical basis. They may entirely disregard palliative effects or prolongation of economic usefulness of patients that may result from treatment, but which cannot be calculated by mathematics.

Although few cancers of the lung may be curable by roentgen therapy and although there still is no satisfactory statistical proof that lives have been definitely prolonged, we have reason to believe from clinical evidence that most patients treated are relieved of distress and that there are no other therapeutic methods so effectual.

Since bronchiogenic carcinomas are histologically pliomorphic, some of the less differentiated cells may be more radiosensitive than others. Therefore, irradiation may destroy the radiosensitive cells, thus reducing the bulk of the tumor and its rate of growth, but the radioresistant cells will not be affected and will continue to reproduce.

Probably the most important benefit derived from irradiation is brought about by the effect on the inflammatory infiltrations that are present in and around the lesion. Absorption of these inflammatory exudates which takes place following treatment may increase the air volume of the lung to some extent and also relieve cough, dyspnea, and pressure pain and at the same time diminish the density and size of the lesion seen radiographically. But this apparent improvement shown radiographically sometimes may be misleading. No doubt the reduction in size and density of the shadows often is due to the absorption of inflammatory exudates which gives the impression that the growth has been influenced to a greater extent than actually takes place. Cough may be caused by pressure of lymph nodes enlarged by inflammation or metastases and these may be reduced in size by treatment, thereby giving relief. Ulcerations and granulations which bleed may be affected when capillaries are contracted and obstructed so that hemoptysis is diminished or stopped temporarily. Since roentgen therapy probably will reduce the inflammation about a bronchiogenic carcinoma, it may be advisable in some cases to give preoperative treatment, thus facilitating the operative procedure.

It is not advisable to give roentgen therapy to every patient with bronchiogenic carcinoma and not infrequently intensive prolonged treatment is unwise. It is useless to treat patients in advanced stages of disease when a large proportion of the lung already is destroyed or when they have severe dyspnea or are cachectic and anemic. The reaction often increases their discomfort and they do not respond satisfactorily. Others in better general physical condition probably had better be treated by moderate intensity only in the hope of giving symptomatic

Those in good physical condition and in stages of disease too advanced for operations may be given intensive prolonged irradiation. Roentgen therapy sometimes is indicated following operation because there is no way of ascertaining whether all the malignant tissues have been excised and if any remains, roentgen therapy may delay its growth. When intensive prolonged irradiation is to be given, it should be remembered that a considerable blood volume passes through the lung during the exposure time and that white blood cells will be destroyed. In addition, a fairly large proportion of the red marrow of the ribs, sternum, and vertebrae is affected so that the production of erythrocytes may be restricted. I have seen a patient whose leukocytes have been reduced to less than one thousand and erythrocytes reduced to two million by prolonged irradiation of the chest. Counts of the blood cells should be made during the course of prolonged irradiation and treatment stopped or modified when there are indications of serious damage. Supportive measures, often including transfusions, should be employed. The possibility of producing pulmonary fibrosis need not give concern.

Conclusions

- 1. The results which may be expected from the treatment of bronchiogenic carcinoma depend primarily upon the extent of disease.
 - 2. If the disease is well localized in the lung, operation is indicated.
- 3. When the disease is too extensive to be completely removable, roentgen therapy is indicated for palliation if the general condition of the patient is such that irradiation therapy can be tolerated.

JOHN F. RENSHAW, M.D.

Gastroscopy is a routine procedure in all cases of gastric ulcer seen in the Section on Gastro-intestinal Diseases at the Cleveland Clinic.

We believe that every case of gastric ulcer should have gastroscopic examinations because gastroscopy serves several purposes. First, it is one more way of confirming the clinical and roentgen diagnosis of benign gastric ulcer. Second, by gastroscopy one is better able to follow the course of the disease and to observe completed healing. Third, the persistence or healing of an associated gastritis may be observed. Fourth, when the clinical or roentgen evidence is not sufficient to make a definite diagnosis of ulcerating carcinoma, gastroscopy may add enough additional data to justify a definite diagnosis of a benign or malignant lesion. We believe, further, that gastroscopy should be done in all patients with negative roentgen findings but with definite gastrointestinal symptoms, especially the ulcer-like syndrome. The following cases represent typical examples of the more common problems which are encountered.

The value of direct visualization in confirming or contradicting the roentgen and clinical diagnosis is shown in the following case.

Case 1: This patient was a forty-eight year old nurse whose presenting symptom was "stomach trouble." She had had distress intermittently for twenty years, characterized by bloating, belching, and occasional sour regurgitations, coming on half an hour after eating. At times there was relief from the use of soda, and at other times a bowel movement would give relief. Laxatives were used frequently.

Physical examination and the routine laboratory tests were negative. The free hydrochloric acid reached a level of 35 units and the total acid 46 units, forty-five minutes after the administration of an Ewald meal.

The first roentgen examination revealed a normal gall-bladder and duodenum. The colon was typical of a spastic or irritable colon, the left half being spastic and the right half atonic. However, an encircling type of filling defect in the pars pylorica due to neoplasm was reported (Fig. 1a).

At gastroscopic examination three days later, the entire stomach was well visualized. The antrum appeared lumpy and thickened and no peristalsis other than one or two very shallow waves was noted. At the lesser curvature of the body, a benign gastric ulcer was seen (Fig. 1b). The gastroscopic diagnosis was benign gastric ulcer on the angulus and severe hypertrophic gastritis.

The patient was placed on ulcer management. Three weeks later the roentgenograms were repeated and reported to be normal. At gastroscopy, however, the ulcer was still seen. The entire antrum was excellently visualized and there was definitely no evidence of malignancy (Fig. 1c). Final gastroscopic examination was done five weeks later, at which time a small, yellowish-white scar was seen at the site of the ulcer.

JOHN F. RENSHAW







Α

В

C

FIGURE 1: a. Encircling type filling defect of antrum.

 Small gastric ulcer, entire antrum including lesser curvature visualized, no evidence of carcinoma.

c. Ulcer almost healed after three weeks of treatment.

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This patient had an atypical history of ulcer. The clinical picture was compatible with the roentgen diagnosis of neoplasm but the first routine gastroscopic examination revealed the diagnosis to be benign gastric ulcer. Subsequent roentgen and gastroscopic examinations were complementary to each other and with both methods the lesion was seen to be benign. Furthermore, the completed healing of the ulcer was accurately observed. The gastritis remained unchanged so that a definite prognosis could be given to the patient. She must be careful of her diet and living habits all her life. And yet, in spite of all precautions, from time to time she will most likely have recurrent distress due to an acute exacerbation of the gastritis. It may be that persons with severe gastritis are more prone to recurrences of peptic ulcer. It also may be that carcinoma is more likely to develop in these patients than in those with normal stomachs. Therefore, we advocate repetition of the gastroscopic examination whenever the patient has recurrence of distress. Even if the patient is free from distress, we believe it is good "health insurance" to repeat the gastroscopic examination once a year.

The value of direct visualization of the lesion is demonstrated in Case 2. This time the roentgen diagnosis concurred with the gastroscopic diagnosis. The value of using both roentgen examination and gastroscopy to follow the course of healing of the ulcer is also emphasized in this case. Exhaustive studies by other workers, particularly Templeton and Schindler¹, have adequately shown this to be true. Both methods are required. One supplements the other, each providing certain information that the other does not.

Case 2: The patient was a forty-five year old restaurant proprietor whose chief complaint was "abdominal distress." The first attack occurred in 1914 and was followed by subsequent attacks in 1918, 1923, and the present one in 1939. Each attack had been characterized by dull, gnawing epigastric pain coming on three to four hours after eating, and relieved by food or rest.

The physical examination was negative. Urinalysis and routine blood tests were essentially normal. With an Ewald test meal, the free hydrochloric acid reached a level of 50 units and the total acid 72 units. forty-five minutes after the meal.

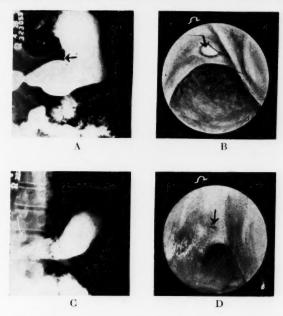


FIGURE 2: a. Suspicious ulcer niche in lesser curvature.

- b. Typical benign ulcer.
- c. Same case five weeks later.
- d. Ulcer almost healed.
- (Permission of W. B. Saunders Co.)

Roentgen examination of the gastro-intestinal tract revealed a normally functioning gallbladder without calculi, the duodenum was normal except for a diverticulum of the third portion, and the colon was spastic. The stomach, however, had a suspicious ulcer niche along the lesser curvature of the pars media (Fig. 2a).

The gastroscopic examination at that time demonstrated a typical, benign gastric ulcer on the angulus (Fig. 2b). Five weeks later the progress roentgen examination of the stomach reported a normal stomach and duodenum except for the diverticulum of the third portion (Fig. 2c). However, at gastroscopic examination on the same day, a small gastric ulcer still was present on the angulus and there was a mild, superficial gastritis (Fig. 2d). The examinations were repeated four months later, and a small, pinhead-sized scar was seen gastroscopically, while the roentgen examination was negative.

In Case 3, the need for doing gastroscopy when the roentgenograms are negative is emphasized. It is interesting to note that this patient had had three roentgen examinations of the gastro-intestinal tract, two of which were done after the ulcer had been demonstrated by gastroscopy, and yet all were negative. This is not a rare experience because in a recent review of thirty-five cases of benign gastric ulcer, three such ulcers were observed gastroscopically. The percentage may be even higher

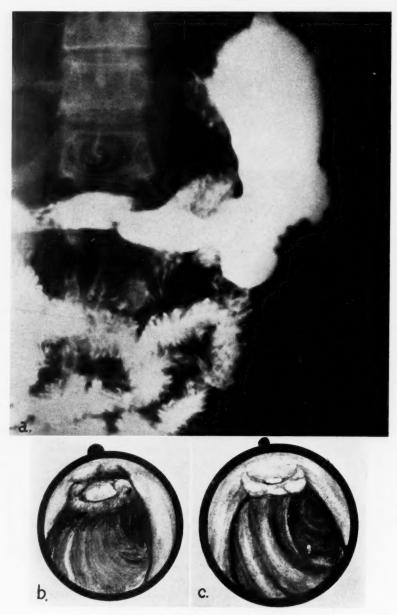


Figure 3: a. Normal roentgenogram.
b. Benign ulcer on angulus.
c. The same ulcer eight days later.

because not all patients with negative roentgen studies have a gastroscopic examination, although they should. Likewise, those same patients are not submitted to exploratory laparotomy, so there is no way to check the negative roentgen findings. Of course, the simplest method, as far as the stomach is concerned, is to do a gastroscopic examination.

Case 3: This patient was a man, thirty-two years of age, who was a spinner in a rayon mill. His chief complaints were a pain in the back, and pain and gas after eating. The present illness began three years previously when dull, localized epigastric pain developed one and a half to two hours after eating. The pain was always relieved by taking some food. On a diet and Amphojel, he had had relief for six to seven months. However, distress recurred shortly after disregarding his diet. He was finally admitted to another hospital for diagnostic study. The roentgen examination revealed normal findings but gastroscopy revealed an ulcer. After twenty days of hospitalization the patient was discharged and was free from symptoms for five months. When the pain recurred, various self-prescribed patent medicines were tried for several months, without much relief. Pain finally developed in the lower dorsal spinal region one and a half to two hours after meals. Frequent feedings seemed to be the only method that gave relief.

Physical examination was negative. The skin was pale. The laboratory tests revealed an anemia and occult blood in the stool. There were 3,880,000 red cells with 74 per cent hemoglobin. Shortly after starting ulcer management, the stools remained negative for occult blood. The blood sugar level was normal and Wassermann and Kahn tests of the blood gave negative reactions. An Ewald test meal elicited 28 units of free hydrochloric acid and 40 units of total acid.

Roentgen examination of the stomach disclosed normal findings except for some hypertrophy of the rugae (Fig. 3a). The duodenum, gallbladder and colon were normal.

The gastroscopic examination revealed a well-defined, moderately deep ulcer on the angulus (Fig. 3b). Two portions of the edge were described as being "cherry red" and probably representing bleeding areas. This was undoubtedly the source of the occult blood in the stool and the cause of the anemia. After eight days of ulcer management, a progress gastroscopic examination (Fig. 3c) revealed a marked reduction in the size of the ulcer and no evidence of discoloration or bleeding about the crater. There was no occult blood in the stools after the second day of ulcer management.

Case 4 was a thirty-four year old clerk whose complaint was "stomach trouble" of two years' duration. He had had more or less daily discomfort for two years. It was characterized by epigastric pain which radiated to the back. The pain kept him awake at night, but once asleep, he would not awaken. Milk or soda did not give satisfactory relief, but milk of magnesia would. The pain became worse as the period after eating became longer. He also had much gas, belching, and general abdominal discomfort associated with nervous tension and constipation.

Physical examination revealed a prematurely gray, hyperkinetic young adult. The peripheral blood vessels were moderately thickened. There was epigastric tenderness but no masses or organs were palpated. The usual laboratory tests revealed normal erythrocyte and leukocyte counts; hemoglobin, blood sugar, and urinalysis were negative. The Wassermann and Kahn tests of the blood gave negative reactions. The basal metabolic rate was minus 14 per cent. Forty-five minutes after an Ewald test meal, the level of free hydrochloric acid was 57 units and the total acid was 75 units.

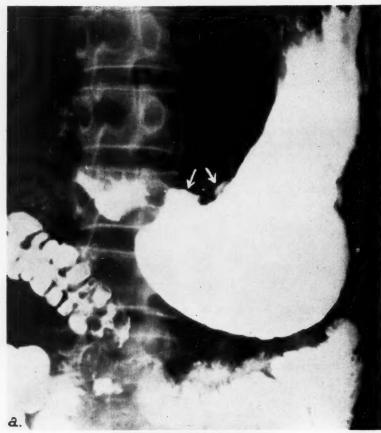




FIGURE 4: a. Large ulcer on lesser curvature of antrum and smaller one in body.

b. Benign ulcer near angulus in body. Ulcer in antrum not visualized. Hypertrophic gastritis was limited to upper parts of stomach.

The roentgenologist reported pyloric obstruction with 60 per cent retention at the end of four hours (Fig. 4a) and 25 per cent at the end of twenty-four hours. An ulcer measuring 1.75 cm. was present in the lesser curvature of the distal pars pylorica. It was associated with marked spasm. There was also a suspicious small ulcer niche in the lesser curvature of the pars media. The gallbladder and colon were normal.

Gastroscopy revealed a benign ulcer on the angulus, associated with severe hypertrophic gastritis in the upper parts of the stomach (Fig. 4b). The pylorus and distal antrum, including the larger ulcer, could not be seen. Not infrequently the lesser curvature of the antrum cannot be visualized and this is one of the technical difficulties of gastroscopy. However, on further analysis of such cases, it has been our experience that gastroscopy usually contributes additional data in spite of nonvisualization of the prepyloric area. In the case reported, the smaller ulcer was definitely benign and the gastroscopic examination further strengthened the clinical opinion that the other lesion was benign.

The patient was hospitalized for strict management. The obstruction was completely relieved within four days. It is interesting to note, however, that the acidity and secretion during the night were difficult to control. It was found by hourly aspirations that two to three times the usual amounts of alkalies had to be used at night in spite of large doses of atropine sulfate. Once complete neutralization was obtained the patient was symptom-free. Two weeks later, progress examination revealed marked decrease in the size of the ulcers. The patient was discharged and instructed to continue the same program at home and to return in four weeks for progress roentgen and gastroscopic examinations.

We believe that every patient who has had a gastric operation for gastric or duodenal ulcer should have gastroscopic examinations if any distress recurs or persists. Case 5 illustrates the importance of this statement.

Case 5: This patient was a forty-five year old dye maker whose chief complaint was "pain in the stomach." The present illness began twenty years previously when a gastro-enterostomy was performed for duodenal ulcer. He was symptom-free for fifteen years, but for the past five years recurring intermittent attacks of pain appeared, characteristically localized to the epigastrium, and coming on two hours after meals. The pain was relieved by taking food or soda. At times, what he described as "tarry stools" had been passed.

Physical examination was essentially negative except for some epigastric tenderness. The routine laboratory tests were normal.

The first roentgen examination in June, 1937, revealed a large penetrating gastric ulcer in the lesser curvature. Three weeks later, progress examination revealed that the ulcer niche was at least a third smaller. Examination four months later showed that the ulcer had not decreased further in size. However, in March, 1938, no niche was present. In July, 1939, sixteen months after the last examination, the patient returned because of recurrent distress. At that time roentgen examination (Fig. 5a) showed a normally functioning gastro-enterostomy with no demonstrable evidence of gastric ulcer other than convergence of folds at the pars media which was the location of the ulcer previously noted.

At gastroscopic examination (Fig. 5b), however, a definite gastric ulcer was seen in the hub of the converging folds. Associated with this was a marked deformity of the stomach due to the scarring and radiating folds. Severe gastritis was also present. The value of the gastroscopic examination in demonstrating the ulcer is apparent in this case.

JOHN F. RENSHAW





B

- FIGURE 5: a. Normally functioning gastro-enterostomy, with no demonstrable evidence of gastric ulcer.
 - b. Ulcer crater on posterior wall portion of stoma with convergence of folds to apex and pseudopolypoid formation.

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Laparotomy was performed on the following patient almost exclusively on the basis of the gastroscopic findings. The clinical picture was that of a benign gastric ulcer which had been present for the past twenty-five years, and the impression of the clinician was benign ulcer. The roentgen examination did not seem to agree with the clinical picture and the roentgen diagnosis was a qualified one of suspected neoplasm. Because of this seemingly incompatible history and roentgen diagnosis and because the ulcer was a gastric one, gastroscopy was indicated. The gastroscopic diagnosis definitely settled the issue.

Case 6: This patient was a woman thirty-nine years of age whose chief complaint was a gnawing pain half an hour after eating. She had been seen for the same complaint approximately eighteen months previously. At that time there was definite clinical and roentgen evidence of duodenal ulcer. She followed ulcer management for five months and was not seen again for eleven months, at which time she had a recurrence of her previous distress. This time, however, it was more severe and there had been a weight loss of thirty pounds.

Physical examination was essentially negative except for an elevated blood pressure. The systolic pressure was 186 mm, of mercury and the diastolic pressure 120 mm, of mercury. There was evidence of marked weight loss but no unusual abdominal findings.

The laboratory examination was essentially normal. The gastric acidity following an Ewald meal was 46 units of free hydrochloric acid and 65 units of total acid.

Roentgen examination revealed the stomach to be normal except for an area of apparent induration or a filling defect at the pylorus. The gastroscopist, however, reported the lesion to be a malignant ulceration in the prepyloric region. The patient was advised to enter the hospital but refused to do so. Ulcer management was carried out at home. The progress gastroscopic examination after one week of ulcer management revealed a benign prepyloric ulcer. The patient continued ulcer management and returned approximately five weeks later for further examinations. At this time the roentgen examination revealed a large atonic stomach obstructed at the pylorus. There was retention of 90 per cent of the barium in five hours. Gastroscopy at this time revealed pyloric obstruction but the ulcer was not seen. The gastroscopist, however, considered the lesion benign but could not definitely exclude a malignancy.

A few days later gastric resection of the posterior Polya type was performed and the pathological report of the resected specimen was acute peptic ulcer with considerable inflammatory reaction.

This case demonstrates the necessity for repeated roentgen and gastroscopic examinations where evidence is not conclusive. Because of the uncertainty of the type of lesion, it was necessary to do repeated examinations, and it was only by this cumulative evidence that a diagnosis could be made.

Conclusions

The cases reported represent typical examples of some of the problems in the diagnosis of gastric ulcer. The need for doing a gastroscopic examination in conjunction with a roentgen examination in every case of known or suspected gastric ulcer is emphasized. It has been our experience that the gastroscopist's diagnosis concurs with the roentgenologist's diagnosis in 80 to 85 per cent of the cases. In the other 15 to 20 per cent which represent the doubtful or incorrect diagnoses made by either method of examination, the percentage of error was almost equally divided between the two. The failure in several instances was due to technical difficulties of the examination. Only a very few cases were incorrectly diagnosed because of improper interpretation and these failures were also divided equally between roentgenology and gastroscopy. Therefore, considering all factors, the roentgen examination remains the most important single examination in gastric ulcer, but gastroscopy is able to contribute such important data in many cases and to further supplement the roentgen examination in other cases, that it becomes an indispensable adjunct to the roentgen examination.

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TRAUMATIC RUPTURE OF THE PANCREAS

Report of a Case

T. E. Jones, M.D.

Traumatic rupture of the pancreas without complicating injury to other abdominal organs is a rare condition and prompts the report of this case. With the recent popularity of the bicycle it may be that we can anticipate an increasing number of patients injured in the abdomen without much evidence of external injury from being struck with the end of the handlebar.

I am indebted to Dr. Norvin Keifer of Geneva, Ohio, for the privilege of seeing this case and for the report of the postoperative care.

CASE REPORT

A white boy, eight years of age, was admitted to the Community Hospital in Geneva, Ohio, at 11:00 a. m., July 23, 1939, with the complaint of having hurt his abdomen in a fall from a bicycle.

The past history was negative except for the usual childhood diseases. He had had convulsions from ingestion of certain foods during infancy and has had a moderate number of gastro-intestinal upsets since that time. Four years ago he had a tonsillectomy, followed by severe postoperative hemorrhage, necessitating a blood transfusion.

The present history dated back one hour, at which time he fell while riding a bicycle. He stated that in turning his bicycle, he had caught the left handlebar in his left trousers pocket and the bicycle had then tipped over in such a manner that the left handlebar was under him while the remainder of the bicycle was on top of him.

There had been no nausea, vomiting, loss of consciousness, or other symptoms except pain, which he had had since the accident. Examination at this time revealed a white boy who was in a moderate amount of shock. The blood pressure was 120/90, pulse rate 110, respiration 22, and temperature 98.0° F. Systemic examination revealed no findings of significance except a moderate amount of tenderness in the upper left quadrant without any rigidity or mass. There was no external evidence of injury. Shortly after the examination, the patient vomited a small amount of undigested food. The blood counts on admission showed 4,390,000 red cells, 32 per cent hemoglobin, and 15,000 white cells with 65 per cent polymorphonuclears. The patient was put to bed for observation and in an hour was quite comfortable. However, the white count had increased to 24,000 with 33 per cent polymorphonuclears.

Three hours after admission the patient complained of a little more pain, the pulse was 130 and blood pressure 112/78. Five hours after admission the condition was unchanged. Abdominal examination showed only a slight tenderness in the left upper abdomen.

Dr. E. H. Merrel was then asked to come into surgical consultation at this time. He agreed that the picture was not of a ruptured abdominal viscus or of hemorrhage and, in view of slight improvement, which was taking place, felt that conservative treatment and observation was indicated.

TRAUMATIC RUPTURE OF THE PANCREAS

The patient had a comfortable night and the following morning his general condition was quite satisfactory. Examination of the abdomen again revealed no rigidity and only slight tenderness in the upper left quadrant. At this time there was visible a very small area of ecchymosis in the left abdomen opposite the umbilicus in the anterior axillary line. The pulse was 160, temperature 100.6° F., and blood counts showed 15,000 white cells with 88 per cent polymorphonuclears.

At 3:00 p. m. in the afternoon, about 30 hours after the injury, the patient became very restless and complained of nausea and difficulty in breathing and began to complain bitterly of severe pain in the left shoulder. At this time the temperature was 101° F., pulse 124. Examination of the abdomen revealed a generalized rigidity which was moderate over the entire abdomen and marked in the upper left quadrant. The white count now was 19.500 with 91 per cent

polymorphonuclears.

At this time it was apparent that an exploratory operation was indicated and I was asked to see the patient. I concurred in the opinion that exploration was indicated and accordingly, at 6:00 p. m., 38 hours after the injury, I opened the abdomen under ether anesthesia. An upper left rectus incision was made. On entering the abdominal cavity, there was a slight amount of serosanguinous fluid apparent. There was no gas in the abdominal cavity, but one was immediately impressed with the multiple areas of fat necrosis throughout the gastrohepatic omentum and the great omentum. Cursory examination showed no injury to the intestines. The spleen was normal and there was no rupture of the liver. Further examination revealed some bloody fluid in the lesser peritoneal cavity and considerable ecchymosis at the root of the mesentery of the small bowel. This was in the region of the superior mesenteric vessels. The lesser peritoneal cavity which was opened between the stomach and the colon revealed a moderate amount of dark bloody fluid. We could then see that there was marked contusion and rupture of the middle third of the pancreas. The contused area was approximately two inches in diameter. There was no occasion to suture the pancreas. Three Penrose drains were placed down to the injured viscus and the abdomen closed with through and through figure-of-eight sutures of chromic catgut. The entire anesthetic period was 45 minutes. The pulse rate of 132 at the beginning of the operation rose to 200 at the conclusion. The patient's condition was not good when he was returned to his room. He was given intravenous glucose, followed by saline hypodermoclysis.

The convalescence ran a very stormy course for about twelve days. On the eighth day, the temperature suddenly rose to 105° F. Nothing was demonstrable in the chest or abdomen to account for the finding. There was profuse drainage of clear pancreatic fluid. At the end of two weeks, the boy's condition was definitely improved. Six weeks after the operation there was a decrease in the amount of drainage of pancreatic fluid but there was a slight amount for four more weeks, a total of ten weeks before it finally ceased entirely. No ventral hernia was apparent at the time of discharge ten weeks following operation. Four determinations of the blood sugar were made during the postoperative course and were found to be normal. On dismissal, the fasting sugar was 103 mgm. After the ingestion of 75 gm. of glucose, the blood sugar was 154 mgm., two hours later it was 124 mgm. The boy's general condition at the time of dismissal was excellent.

It is conceivable that there may be many injuries to the pancreas of a lesser degree that may recover spontaneously after days or weeks of illness, with the resultant cyst formation in later years.

T. E. JONES

In reviewing the literature, the symptoms calling for operation may occur at varying periods from days to weeks and this, of course, is in direct relation to the amount of damage done to the pancreas. When there has been sufficient leakage of pancreatic juice to cause fat necrosis, the abdominal signs and symptoms of pain and rigidity rapidly result. It is also worthy of note that all cases have a very severe reaction post-operatively similar to this case for days up to a week or so.

SUMMARY

The significant points in the case reported are the severe injury produced to the pancreas with only a small ecchymotic spot as external evidence of injury and the keen observation of the attending physician at frequent intervals following the injury. His prompt recognition that a sudden change had taken place calling for early surgical intervention was instrumental in saving the boy's life.

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THE USE OF QUINIDINE FOR AURICULAR FIBRILLATION IN HYPERTHYROIDISM

A. CARLTON ERNSTENE, M.D. and R. S. DINSMORE, M.D.

Auricular fibrillation occurs, either in its continuous form or in paroxysms of long or short duration, in about 10 per cent of all patients with hyperthyroidism. The preoperative treatment of these patients consists of the usual measures plus the administration of digitalis in sufficient amounts to reduce the heart rate to approximately 90 beats per minute. During the period of preparation for operation, no attempt is made to re-establish the normal heart rhythm. In approximately one-half of all patients with hyperthyroidism and auricular fibrillation, the heart rhythm spontaneously becomes regular during the first week or ten days after subtotal thyroidectomy, and normal rhythm can be restored in nearly one-half of the remaining patients by the use of quinidine sulfate.

CASE REPORT

The following case report illustrates the successful use of quinidine sulfate in the treatment of auricular fibrillation which persisted after thyroidectomy.

The patient, a white man fifty-four years of age, was admitted to the hospital on October 23, 1939 because of nervousness, palpitation, and loss of weight. The loss of weight had begun about six months earlier and had amounted in all to about thirty pounds. About three months previous to admission he began to get extremely nervous. Along with this, there was loss of strength, trembling of the hands, and profuse perspiration. The basal metabolic rate was plus 19 per cent in July, 1939. A diagnosis of hyperthyroidism was made at that time. The patient was placed on a two weeks' course of Lugol's solution, followed by Iodosin from that time on. In addition to this he had been given digitalis and during August and September he also had received eight weekly treatments with roentgen therapy. He felt that he had received some benefit from these treatments.

The past medical history was negative except for the usual childhood diseases and an appendectomy in 1931.

Physical examination revealed a thin, nervous individual sixty-five inches tall, weighing ninety-five pounds and with a flushed, moist skin. The thyroid gland was firm and only slightly increased in size. The heart was not enlarged and no murmurs could be heard. Auricular fibrillation was present with an apex rate of 88 and a radial rate of 76. The blood pressure was 120 mm. systolic and 82 mm. diastolic.

A diagnosis of diffuse goiter with hyperthyroidism and auricular fibrillation

An electrocardiogram showed auricular fibrillation with a ventricular rate of 92 per minute. The Q.R.S. complexes were normal and the electric axis likewise was normal. There was slight depression of the S-T intervals in Leads II, III and IV F.

Roentgenograms of the chest showed nothing abnormal. Urinalyses and blood counts gave normal findings.

The patient was placed on the usual routine of Lugol's solution, high caloric diet, sedatives, and digitalis. On the morning after admission to the hospital the basal metabolic rate was plus 38 per cent. Eight days later the rate had dropped

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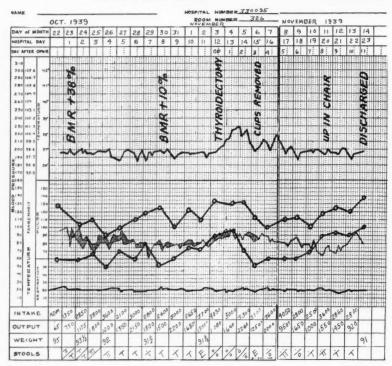


FIGURE 1: Clinical chart.

to plus 10 per cent, and on the twelfth day a subtotal thyroidectomy was done. The gland was only slightly larger than normal and the portion removed weighed 17 grams. On section the gland was homogeneous throughout, finely lobulated, and contained very little colloid. No adenomas were seen. The microscopic diagnosis was moderate hyperplasia.

Postoperatively, the patient had very little reaction, although the temperature on the second night was 101.3. The heart rate did not rise above 100 beats per minute. Digitalis was continued in daily maintenance amounts. Auricular fibrillation persisted, and on the eighth postoperative day the patient was given quinidine sulfate, 3 grains, followed by a second dose of the same size two hours later. The heart rhythm became regular one hour after the second dose. An electrocardiogram taken shortly afterward showed sinus rhythm with a rate of 80 per minute. Except for rather marked depression of the S-T intervals in Leads II, III and IV F, the tracing was normal in all respects.

DISCUSSION

During the period of preparation for operation, the administration of quinidine sulfate for auricular fibrillation serves no useful purpose, because even though normal rhythm is restored, the arrhythmia almost

QUINIDINE FOR AURICULAR FIBRILLATION IN HYPERTHYROIDISM

always recurs promptly. In those patients, however, in whom auricular fibrillation persists for more than a week after subtotal thyroidectomy, an attempt should be made to re-establish normal rhythm unless some contraindication for the use of quinidine sulfate is present. The principal contraindications for employment of the drug are the presence of a considerably enlarged heart, the presence of valvular heart disease, particularly mitral stenosis, a history of earlier embolic accidents and a history of sensitiveness or idiosyncrasy to quinine or quinidine. When these restrictions are observed, the drug can be given with safety. to five doses are given each day at intervals of two hours, and the size of the individual dose is gradually increased until a total daily dosage of 30 grains is reached. In the successful cases, normal rhythm usually is re-established within the first three days of treatment, but when auricular fibrillation persists, the drug is continued for one week before admitting failure.

In this schedule of treatment the administration of quinidine is begun if auricular fibrillation persists for more than one week after subtotal thyroidectomy. It is true, of course, that in a certain number of patients normal rhythm would be re-established spontaneously if a longer interval were allowed. The time for beginning the use of quinidine has been chosen arbitrarily in order not to prolong the period of hospitalization. Quinidine should not be given to ambulatory patients, and while the use of the drug within such a short time of the operation results in its being given to more patients than would otherwise be necessary, it has the advantage of avoiding a later period of hospitalization for quinidine therapy for a larger number of individuals.

After normal cardiac rhythm has been re-established, subsequent reversion to auricular fibrillation occurs in only a rare patient. In individuals beyond the age of forty-five years, however, it appears advisable to continue quinidine in doses of 3 grains twice a day for two to four weeks on the assumption that reversion to the arrhythmia is most liable to occur during this time.

NEUROGENIC BLADDER ASSOCIATED WITH BRAIN TUMORS

With Presentation of a Case Study
W. James Gardner, M.D.

Until fairly recently, the top level for the control of the autonomic functions of the body has been assumed to be the basal ganglia of the brain. The work of experimental physiologists, particularly Sherrington, Denney-Brown, and Robertson in England, Fulton, Bucy, Langworthy, and Kolb in America has proved conclusively the existence of autonomic representation in the cerebral cortex. These highest autonomic centers are located in the cortex of the frontal lobes and they exert a governing effect on the centers in the hypothalamus and medulla which regulate visceral activity. Blood vessel tone, glandular secretions, sweating, and gastro-intestinal motility are a few of the visceral functions which have been proved to be definitely under the control of the frontal lobes of the brain.

In a study on the physiology of micturition in man, Denney-Brown and Graeme Robertson observed the variations in intravesical pressure which occur with increasing distention of the bladder. They concluded that apart from a faint background of maintained tonic activity, spontaneous vesical activity takes the form of waves of contraction appearing in rhythmical progression. An effort to void evokes powerful contractions of the bladder, whereas a voluntary effort of restraint completely inhibits the nervous discharges responsible for spontaneous vesical activity.

In pursuing the center for micturition cephalad, Longworthy and Kolb studied intravesical pressures in normal animals and in animals with sections through the brain stem at various levels. They first established the volume of contents necessary to induce reflex micturition in the intact animal. They found this to be 155 cc. in the cat. After removal of the motor cortex on one side, this volume was reduced to 30 cc. After removal of the other motor cortex, the volume was further reduced to 20 cc. After a section at the upper border of the pons, it was 11 cc. When the section was at the middle of the pons or below, reflex micturition was very weak and incomplete. That is, there was retention with overflow. The conclusions to be drawn from these findings are that tone in the musculature of the bladder is similar to tone in striated muscles, that it is under the control of the motor cortex which exerts an inhibiting action on the reflex centers in the cephalic portion of the hind brain.

The bladder symptoms of patients with cerebral lesions have not received very serious consideration in medical literature. The reason for this is probably that the incontinence has been dismissed under the assumption that it was a mental symptom. Although this is true perhaps in the majority of cases, it certainly is not true in all instances.

NEUROGENIC BLADDER ASSOCIATED WITH BRAIN TUMORS

Every neurological surgeon has observed retention of urine in certain patients with cerebellar tumors. This is the result of pressure on the medulla with interruption of the reflex arc to the centers in the upper portion of the pons. With this arc interrupted, the tone of the bladder musculature is lost. This was demonstrated experimentally by Langworthy and Kolb by their sections through the middle of the pons.

It is well recognized now that true vesicle incontinence can occur as a result of lesions of the frontal lobes. Our experience seems to indicate that the lesion must affect both frontal lobes, although exactly what portion must be damaged is not entirely clear. We have seen it in unilateral frontal lobe tumors which were of sufficient size to markedly compress the opposite frontal lobe. It has always cleared up with removal of the tumor even though this involved amputation of one frontal lobe or even removal of an entire cerebral hemisphere.

The patient who has elicited our greatest interest in this problem is one in whom it was necessary to amputate both frontal lobes for an infiltrating tumor.

This patient was a woman of 52 years who presented a typical picture of brain tumor and who in addition was incontinent of urine. The significance of this symptom was not realized at the time of her original study and it was ascribed to intellectual deficit. Ventriculography indicated the presence of a bilateral frontal lobe tumor. At operation on August 28, 1933, an infiltrating tumor of the right frontal lobe was found and an amputation of this lobe was performed at a point anterior to the motor area. The patient immediately became continent but lapsed again into incontinence seven days later. As the first operation showed the tumor extending into the left frontal lobe, this lobe was amputated at a second operation 12 days later. The patient made a satisfactory recovery from these operations but has remained absolutely incontinent to date. The patient is rational. She shows some memory defect and complicated mental processes are impossible. She, however, is tidy about her appearance and in her habits. She is never conscious of a feeling of fullness in the bladder and even when it is full, voluntary urination is impossible. The urine does not dribble. It discharges involuntarily after several hours of filling. She has never been catheterized to determine whether or not there is retention.

Cystoscopic study was performed by Dr. Higgins. His notes are as follows: Cystoscope passed with ease. There is no loss of sensation in the urethra. Hot water was allowed to run into the bladder which the patient could differentiate from cold solution. The bladder is quite atonic but there is no fine trabeculation present. Upon irritating the wall of the bladder with a catheter there was but very little response. The internal sphincter shows a marked degree of loss of tone.

Here, then, we have the picture of a patient who cannot tell when her bladder is full and cannot voluntarily empty it. This, in spite of the fact that there is no paralysis and no loss of cutaneous sensibility. These findings are in agreement with the experimental evidence that the centers for voluntary control of micturition are located bilaterally in the frontal lobes.

FACTORS RESPONSIBLE FOR THE LOWER MORTALITY IN PROSTATIC SURGERY

W. J. ENGEL, M.D.

That the mortality in prostatic surgery has been reduced sharply in recent years has been repeatedly demonstrated by the published statistics of various clinics, and we have shared in this experience. The advent of transurethral resection marked the turning point. In reviewing our statistics, the average mortality over a period of years prior to resection was 8.9 per cent whereas, in a like period since resection, the average mortality has been 1.8 per cent. Although resection is unquestionably the largest single factor responsible for this favorable trend, I feel there are other factors which should be given due credit in the consideration of this subject, which may be discussed under the following headings:

- 1. Earlier diagnosis and acceptance of treatment.
- 2. Preoperative preparation.
- 3. The operation itself.
- 4. Postoperative care.

EARLIER DIAGNOSIS AND ACCEPTANCE OF TREATMENT

In recent years, I have been impressed with the fact that we are seeing patients with bladder neck obstruction earlier in the course of the disease. More patients are coming in immediately following their first attack of urinary retention, and many are presenting themselves for relief of symptoms of urinary obstruction before they have progressed to the stage of complete urinary retention. I believe this is attributable in the main to two factors. First, the general physician is to be congratulated for recognizing symptoms of bladder neck obstruction earlier and advising corrective surgery. As a result, the layman has gradually learned that obstructive urinary symptoms are not just a necessary torment of old age, but the manifestation of a disease that may be remedied. Second, there can be little doubt that in the patient's mind, fear of operation, in years past, has been the greatest deterrent to accepting early operation. Today, however, the layman himself has become aware of the greater safety in prostatic surgery, and this confidence prompts him to seek operative relief at an earlier date. Gone is the treacherous hatband catheter and rare indeed is the patient who practices self-catheterization in preference to operation.

As a direct result of this earlier acceptance of operation for bladder neck obstruction, we are naturally operating upon better risk patients and fewer with advanced renal damage from prolonged back pressure. An important corollary to early treatment is the fact that the glands are smaller and are, therefore, more suitable to relief by transurethral resection, so that in the past several years I have found that approxi-

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mately 90 per cent of the cases can be relieved by resection while only 10 per cent are of such large size that prostatectomy is necessary. Of especial interest to me is the fact that the patient's confidence in all prostatic surgery has been increased and they accept advice for prostatectomy as readily as for resection.

PREOPERATIVE PREPARATION

Certain essentials in the preoperative study of the prostatic patient, such as adequate blood chemistry studies and renal function tests, have long been known and so firmly established that they merely need to be mentioned here. If renal function is impaired, corrective measures must be instituted before operation can be carried out safely. More recently, however, we have learned to depend upon intravenous urography for guidance, not only as to the functional capacity of the kidneys, but also as an aid in prognosing the surgical convalescence. In general, it may be said that prompt function and a normal delineation of the upper urinary tract encourages one to predict an uneventful outcome, while delayed function with bilateral dilatation of ureters and kidney pelves is a warning that the patient requires deliberate and careful preoperative preparation if he is to be carried safely through the operation.

In 1939¹ I called attention to the preoperative prostatic mortality and showed at that time that a significant number of patients died during the course of preoperative preparation and that by revising the preoperative management, we were able to sharply reduce the number of preoperative deaths and indirectly to influence favorably the mortality following surgical operation. At that time attention was drawn to the dangers associated with urethral instrumentation in prostatics, particularly undue urethral trauma at the moment of first urinary retention, the inlying urethral catheter, and also diagnostic cystoscopy. The danger lies in the increased susceptibility of the obstructed urinary tract to infection which may be initiated in one of these ways.

Certainly, one cannot overemphasize the importance of the first contact with the patient who has acute urinary retention, for it may be the first chapter of a story with a happy ending or the beginning of a tragedy. The one great watchword should be gentleness which must be combined with an adequate instrumentarium and a scrupulous aseptic technic. Attention to these details, which must be observed especially by the general physician, can be one of the greatest factors in reducing the prostatic mortality still further. In this connection it seems well to discourage the use of the rigid metal catheter as it is an instrument of extreme danger. If a soft rubber catheter will not pass, it is much wiser to employ a semirigid silk woven instrument and to remember that no instrument should be forced—merely passed.

The value of adequate preoperative drainage in increasing the safety of prostatic surgery has, of course, long been recognized, and the use of the inlying catheter for this purpose is rather firmly intrenched in the mind of the physician. We, however, have convinced ourselves that this method of preoperative drainage possesses a hazard which can be avoided. It not infrequently is responsible for setting up urinary infection which, even if the patient recovers, is very debilitating; but worse, may even prove fatal. Our experience justifies the conclusion that the avoidance of the inlying catheter has been a large factor in increasing the safety of prostatic surgery. As a substitute, we prefer intermittent catheterization, or if more prolonged and continuous drainage seems necessary, suprapubic puncture is done, the technic of which was described in the article previously referred to.¹

In summarizing our present method of preoperative preparation, which we believe has been of importance in reducing the prostatic mortality, the patients may be divided into four groups.

The first group includes patients in whom no inlying catheter and no other type of catheterization is employed. This includes those who present themselves with definite symptoms of obstruction but who never have had complete urinary retention. In such cases where the residual urine is not large and the renal function is satisfactory, as measured by urea clearance, other kidney function tests, or intravenous urogram, preliminary catheter drainage is not required and operation may be carried out safely the day after entrance into the hospital.

In group two are those patients who are prepared by intermittent catheterization. This group includes the patients with recent, acute retention in whom we prefer to carry out intermittent catheterization, this being done every six or eight hours or more often if the case demands.

The third group is comprised of those who present themselves with chronically overdistended bladders and with rather severely impaired renal function, in which we feel that a prolonged period of drainage is necessary. Suprapubic puncture has been more preferable in this group of cases.

In the fourth group is a very small number in which the inlying catheter is still employed, and ordinarily constitutes only those patients who are sent to us wearing inlying catheters, together with the rare patient with a severely infected and contracted bladder in whom suprapubic puncture cannot be done.

We have been impressed with the fact that preoperative management of patients according to this plan has markedly reduced the preoperative mortality and has certainly resulted in a smoother postoperative convalescence and a lower operative mortality. The risk of infection from wearing the inlying catheter condemns its use and undoubtedly its elimination has distinctly reduced the mortality in prostatic surgery.

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In order to evaluate the success of this method of preoperative management, I recently reviewed one hundred consecutive cases managed by this plan. The ages of this group of patients are shown in Table 1, from

Age o	of Patients
50-59	
60-69	39
70-79	41
80-89	8

which it will be seen that the usual age group of prostatics is included, the highest number occurring in the eighth decade.

Of this group of one hundred patients, ninety-two had transurethral resections and eight had suprapubic prostatectomies. No catheterization was done in twenty-six cases. The preoperative period was only one day in nineteen cases and two days in the remaining seven. The longest postoperative period was ten days while nineteen of the twenty-six cases were in the hospital seven days or less following operation, all cases having had prostatic resection. No operative deaths occurred in this group and no noteworthy complications were noted. The range of blood ureas is shown in Table 2, from which it is seen that only patients without significant urea retention are selected for this type of management.

TABLE 2

	No Catheler	Intermittent catheter- ization	Supra- pubic puncture	Inlying catheter
Cases	26	53	16	5
UREA (mg. %)				
30-40	10	17		1
40-50	12	14	3	2
50-60	4	10	4	
60-80		8	1	1
80-100		4	3	1
100-150			3	
150-200			2	

There were fifty-three patients who had intermittent catheterization. We believe this is less likely to be followed by urinary infection, particularly if done at regular intervals without allowing the bladder to become overdistended. Of this group, five had prostatectomies and the remaining forty-eight had resections. Twenty-seven cases or 51 per cent spent only one or two days in the hospital before operation and in the remaining twenty-six the preoperative period ranged from three to seven days, the higher ureas requiring the longer periods of preoperative preparation.

Suprapubic puncture was carried out in sixteen of the hundred cases. When first seen the majority of these patients had large, palpably distended bladders reaching almost to the umbilicus. It is particularly this type in which we advocate suprapubic puncture as a means of avoiding infection which plays such havoc, once introduced. As will be seen in the table, the higher blood ureas occurred in this group and therefore a longer period of preoperative drainage was required. In fact, six of the sixteen patients were sent home wearing a suprapubic catheter for a period of from three weeks to two months, and we encourage all patients to do so in whom we believe a long period of drainage is essential. The remaining ten patients in this group were operated upon after seven to fourteen days of drainage. Fourteen patients had resections and two had prostatectomies.

There were only five patients in whom an inlying catheter was used and in every instance it had been inserted elsewhere. Resection was performed in four of these and prostatectomy in one, and all recovered satisfactorily.

We feel that this plan of preoperative preparation has been one of the most important factors, not only in reducing the preoperative prostatic mortality, but also in reducing the operative mortality.

THE OPERATION ITSELF

As has already been stated, there can be little question that transure-thral resection has been the greatest single factor in reducing the operative mortality in prostatic hypertrophy. It is true, of course, that the mortality statistics of this operation will depend to a large extent upon the experience of the surgeon and it is equally true that as experience has increased, the safety of the operation has also increased, as has also the completeness of the resection. Contributing to the greater safety of prostatic resection is the fact that the confinement to bed is shortened tremendously. Most patients having this operation spend only two to three days in bed, as it has always been our practice to allow patients up just as soon as the urethral catheter is removed. Another factor undoubtedly contributing to the safety is the improvement in methods of anesthesia, and it is my own personal belief that spinal anesthesia has

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contributed greatly to the safety of operation. We have found that otherwise bad risk patients with cardiovascular disease and other associated complicating conditions tolerate spinal anesthesia exceptionally well, and I am convinced that there is less hazard in this than in inhalation anesthesia, or anesthetics of other types.

One of the early hazards of transurethral resection, namely hemorrhage, has been almost entirely eliminated and in the present day of resection it is rare indeed to see a patient in whom hemorrhage constitutes any threat to recovery. This, of course, is due in large part to improved cutting and coagulating currents, but its incidence diminishes as the experience of the surgeon increases.

I have previously indicated that there is approximately 10 per cent of patients in whom we feel that prostatectomy is still the operation of choice. It has been interesting to observe, however, that the mortality from prostatectomy has also diminished and this, I feel, is indirectly due to resection. This apparently contradictory statement is explainable because of the fact that since the advent of transurethral resection, we may be much more selective in patients for whom we advise prostatectomy, choosing only the better risk patients with a large gland. In such cases, we have been able in every instance to perform a one-stage suprapubic prostatectomy, and since 1933 there have been under my care thirty-four prostatectomies without a death. Although suprapubic prostatectomy has been our preference, those who advocate perineal prostatectomy likewise have reported a diminishing mortality rate.

It is thus seen that, irrespective of the type of operation selected for the patient, the lower mortality obtains.

POSTOPERATIVE CARE

In consideration of postoperative care, the question arises as to what is the common cause of postoperative deaths which have occurred following prostatic surgery. I should like to consider first the postoperative deaths following prostatic resection. In reviewing the operative deaths from resection, the one fact that stood out was that 56.2 per cent were due to postoperative urinary sepsis with resultant uremia. This fatal complication has been largely controlled by two measures, (1) the institution of a closed system of postoperative irrigation and (2) by the use of the newer chemotherapeutic agents. In crediting closed irrigation one needs only to observe the striking reduction in this complication following its institution some years ago. Whereas urinary sepsis was a relatively common postoperative complication before the adoption of closed irrigation, this complication now is exceedingly rare and when it does occur, it is ordinarily mild and easily controlled with one of the newer chemotherapeutic agents, particularly sulfanilamide and sulfapyridine.

Another important measure in postoperative care to which we attach significance is the early removal of the inlying catheter. The catheter should be removed just as soon as all risk of hemorrhage is passed, which, in many cases, is at the end of twenty-four hours and never later than forty-eight hours. The same objection to the preoperative use of the inlying catheter holds for its postoperative employment, and to leave it in beyond forty-eight hours is to invite trouble. Its early removal not only tends to reduce the risk of postoperative urinary sepsis, but also sharply reduces the incidence of epididymitis and other complications, and enhances the comfort of the patient. If the resection has been adequate, we feel there is no need to leave the catheter in beyond the time the danger of bleeding is passed, and its early removal avoids many difficulties. As previously stated, we insist upon the patient getting out of bed as soon as the catheter is removed and this early increase of normal activity lessens the chance of pulmonary complications.

In considering the postoperative care of the patient who has had a prostatectomy, there have been no significant changes in the routine which has been employed for a long period of time. Because continuous through and through irrigation may be carried out, the danger of urinary sepsis is not so great as following prostatic resection. The usual causes of death following prostatectomy have been, in the past, shock, circulatory failure, renal failure and pneumonia. These have been largely removed because we are now able to select better risks for this operation.

In summary, we believe that today there is a changed outlook for the prostatic patient who faces operation, and he can contemplate it with much less fear. Whether or not the ultimate in safety of this operation has been reached is difficult to say, although it must be admitted that there must be some end-point. Where one is carrying out a surgical procedure on patients in this age group, it would seem that a certain mortality is inevitable, but it should be our constant aim to seek improvement until this mortality has reached its lowest possible level.

REFERENCE

Engel, W. J.: Preoperative prostatic mortality, J. Urol. 41:505-514, (April) 1939.

CHRONIC URTICARIA AND ANGIONEUROTIC EDEMA

Case Reports and Observations

C. R. K. Johnston, M.D.

Urticaria is a lesion familiar to almost everyone and has been described in the medical literature since the time of Hippocrates. Yet the cause of chronic hives is frequently baffling and the treatment often unsatisfactory. No therapy may be necessary for acute hives, although abstaining from food for twenty-four hours, purgation and adrenalin hypodermically will probably result in more prompt relief. Chronic urticaria presents an entirely different problem, as is illustrated in the following case reports. No attempt is made to distinguish between urticaria and angioneurotic edema except in diagnosis, because the lesion is essentially the same in either case. In fact, both frequently occur in the same individual and the causes and treatment are similar.

Case 1: The patient was a housewife twenty-six years of age, who complained of recurring attacks of localized edema for the past three years, involving the feet, hands, fingers, arms, lips, and eyelids. The attacks occurred ten to fourteen days prior to the menstrual period and lasted about five days. The areas were painful and at times blood was vomited during the attacks. She felt sure that taking aspirin would precipitate an attack. The personal history otherwise was negative for allergic disease. Her father had similar attacks of edema, which he attributed to the use of aspirin.

Physical examination was relatively negative. Routine blood counts and urinalysis were normal. Roentgen examination of the gastro-intestinal tract showed a normal stomach, gallbladder and colon.

Allergy studies revealed sensitivity to feathers, house dust, orris root, brewer's yeast, cow's milk, corn, cherry, plum, and to several other less frequently used fruits and vegetables.

On a program of avoidance of the inhalants and foods to which she reacted, as well as the drug she suspected, she became free from symptoms. A letter two years later stated that she had slight attacks of swelling only when she failed to follow the allergy diet. She was using goat's milk as a substitute for cow's milk. The angioneurotic edema in this case was apparently due chiefly to foods, though a drug (aspirin) would precipitate an attack also.

Case 2: The patient, a woman twenty-five years of age, was seen in April. 1938, complaining of headaches and hives. The headaches had been present for some time, but for the preceding six months they had been very severe, lasting three days and recurring about twice a month. She usually had a headache during or after the menstrual period, and a second headache in the intermenstrual period. They were the hemicrania type, and accompanied by no gastro-intestinal upset except for a tendency to constipation during the attacks. The hives, which were usually on the face, neck, and arms, had been present almost daily for several years. As a rule, the lesions were few and lasted only a few hours, although they were quite itchy and annoying. She also exhibited a tendency at all seasons for easy sneezing, nasal obstruction and postnasal mucoid discharge. Her mother and sister had similar headaches, while her father and a maternal aunt suffered from asthma.

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Physical examination was entirely negative. The routine urinalysis and blood counts were negative except for a mild anemia (hemoglobin 69 per cent). The eosinophil count was 2 per cent.

Allergy investigation revealed sensitivity to numerous inhalants, including feathers, dust, orris root, tobacco, silk, and several animal danders. The food reactions were quite marked to wheat, white potato, pineapple, brewer's yeast, cherry, strawberry, and Brussels sprouts, and less marked reactions to egg, milk, and many others.

On a regime of avoidance of the significant inhalants and foods, she made marked progress. Three months after beginning the regime, she reported that she had had no hives, and the headaches were much improved. Those headaches she had had could be attributed to a break in her diet.

Twenty-two months after the institution of the allergy program, she was still free of hives. She had had only one attack of giant hives, this following the ingestion of three empirin compound tablets. The headaches also were completely gone except on a few occasions when she broke her diet. She had found that eating white potatoes or wheat would result in headaches, as well as hives. Both the migraine and urticaria in this case could be attributed to foods. A drug (empirin compound) had also precipitated an attack of hives on one occasion.

Case 3: The patient, a woman twenty-six years of age, complained of swelling of the lips, the right side of the forehead and the right forearm. The swelling had been present almost three years and occurred in close relation to the menstrual period, either just before, after, or during the period. Headache and nausea always accompanied the attacks. About one year prior to her visit, following an attack of pain in the right side, she had the appendix and right ovary removed. From the time of the operation to the present attack she had had only one subsequent attack of angioneurotic edema. Various elimination diets in the past had failed to help.

With the exception of the areas of angioneurotic edema, physical examination was entirely negative, as were the routine blood counts and urinalysis.

Because of the obvious relationship of her attacks to the menstrual periods, allergy tests were omitted and glandular therapy given a trial. She was advised to have 1 cc. of antuitrin S (100 units per cc.) daily for five to seven days, beginning about ten days before the period was expected. This was carried out for two consecutive periods, during which time no swelling occurred. The therapy was stopped and she remained free from attacks for the next three months as well. The edema then recurred, involving the same three sites as before. She was advised a similar program, this time using A. P. L., (Ayerst, McKenna, and Harrison) in doses of 1/5 cc. (500 units per cc.). For approximately five months this program was continued. About five doses of the A. P. L. preceding each period were taken, and she remained free of edema. This freedom continued for five months after taking the last dose of A. P. L. when once more the edema recurred in the same areas. She was again advised to resume the same type of therapy and has not returned, although over a year has elapsed since the last visit. This patient's angioneurotic edema was controlled by treating only the endocrine factor.

Case 4: The patient, a man aged forty-two, came to the Clinic because of hives and headaches. The hives had begun some three and one-half years previously, at which time he was in apparently good health. He was an auditor and was working hard and under considerable nervous tension. Attacks had occurred almost every day since the onset, the only free period being for one or two days while on a brief vacation. The hives were generalized at first; later

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they recurred more often on the back and upper chest. No angioneurotic edema was present. The hives were worse during the day, while at work, and bromides would give some relief.

He took a proprietary preparation, containing antipyrine, potassium bromide and sodium salicylate, one or more times per week for headache but used no other drugs. An interesting observation was that he had seen thirteen doctors for the above complaint before consulting the Clinic. He had found that eating eggs would cause hives but no other foods were suspected.

Since childhood he had had severe generalized headaches, recurring on the average of once a week, and lasting about twenty-four hours. Until some fifteen years ago they had been accompanied by nausea and vomiting. Since then nausea occurred but rarely. Substituting kapok pillows for feather pillows had resulted in some improvement and wearing glasses also helped, but the headaches continued.

The personal history was otherwise negative for allergy. His mother had "sick headaches," and her mother and brother had asthma. A paternal aunt had hay fever.

Physical examination revealed a well developed and nourished, apparently healthy individual. Several urticarial wheals were present on his back and his skin exhibited a mild dermographia. The physical examination otherwise was not significant.

Dental examination revealed a retained root, one devitalized tooth, and two molars which showed questionable apical involvement. Routine blood counts and urinalysis were normal. Blood eosinophilia was not present.

Allergy studies by the scratch method were all negative. Intradermal tests showed immediate reactions to many inhalants, including kapok 3+, house dust, feathers, orris root, tobacco, silk, cat and dog dander 2+, and 1+ readings for pyrethrum, mattress dust, yeast and several molds. Delayed reactions were 2+ to oidiomycin and 4+ to trichophytin. No significant reactions were obtained to bacteria. Many positive food reactions (chiefly 1+) were found, including corn, oat, pork, duck, goose, turkey, coffee, tea, chocolate, the berry group, onion, asparagus, mushroom, nuts, canteloupe, cucumber, watermelon, and olives.

A very careful program of treatment was outlined, including avoidance as far as possible of all inhalant and food allergens. He was instructed to avoid rigidly the use of the proprietary he had been taking and all other drugs. Hyposensitization therapy was begun for the inhalant allergens, including dust, feathers, orris root, kapok, tobacco smoke and ashes and the significant molds, all in a 1:10,000 concentration. He was strongly advised to obtain extra rest, have the dental foci removed, and was temporarily given a sedative of bromides and belladonna.

One month later the patient stated that his headaches had ceased and that the hives were much improved. Further extract was supplied and the above program continued.

Five months after beginning this treatment, the patient returned and reported that he had only an occasional hive and seven to ten days would pass without any at all. The headaches were almost entirely absent, although an occasional, mild ache still occurred. He reported one severe flare-up in hives after a dose of concentrated extract (1:10) and he had found that inhalation of tobacco smoke or orris root would precipitate an attack of hives in about half an hour.

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In this case the urticaria may have been due to one or several factors. Food and inhalant allergy seem definitely incriminated, but a proprietary, fatigue, and focal infection may also play a definite role.

DISCUSSION

In cases of urticaria and angioneurotic edema, skin tests are admittedly of less value than in other allergic diseases. Investigation of patients complaining of either of these lesions must be very thorough, and all possible factors should be treated if one is to achieve satisfactory results. In a small number of cases, the history may strongly incriminate a significant factor, such as the endocrine factor in Case Three, or some drug frequently taken by the patient. Skin tests may be postponed in such a case until a trial of removal of the suspected food or drug or control of the glandular factor has been attempted and if successful, allergy tests may not be necessary. Seldom, however, is the problem solved so simply.

When the history indicates the coexistence of one or more allergic manifestations (Cases 2 and 4), or a family history of allergy (Case 1), the greater is the likelihood that the case under investigation will prove to be on an allergic basis. Such allergy usually is dependent on food, drug, or bacterial sensitivity, but occasionally it may be due to inhalants or physical agents. The foods commonly incriminated include milk, eggs, wheat, chocolate, shellfish, and many others. Drug allergy is frequent and includes many widely used drugs, such as aspirin and other salicylates, phenolphthalein, quinine, ipecac, barbiturates, opium derivatives, iodides, etc. Focal infection is undoubtedly a common cause of chronic hives and it may be explained on a basis of bacterial toxins or bacterial sensitivity. Search should always be made for foci in teeth, tonsils, sinuses, gallbladder, appendix, prostate, etc. In some cases where no focus can be found, we have had considerable success with bacterial vaccines made from stool cultures.

When the personal and family history are entirely negative for allergic disease, many allergists believe that drugs or foci of infection are the most likely causes. The psychogenic factor is also important. It may at times be primary, and frequently is a contributing factor of significance. I feel that thorough testing should be carried out in these cases, however, as food or other allergy also may be present and its removal will lighten the "allergic overload." It is not infrequently noted that certain foods will cause an increase in symptoms, although the removal of these foods from the diet may not result in disappearance of all hives. The endocrine factor is probably not of great significance as a primary cause although it may contribute secondarily in many cases in the form of lowered metabolic rate, for example, or in women nearing the menopause.

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In conclusion, I should like to emphasize that chronic urticaria or angioneurotic edema may have many causative factors, either primary or secondary. A few illustrative case reports have been given, although needless to say, the conclusions are by no means based on these alone.

It seems worthy of emphasis that when a personal or family history of other allergy exists, the cause of hives or angioneurotic edema is more likely an allergic one. In the absence of any allergic history, drug allergy or focal infection are very frequent offenders. The psychogenic factor is an important one, although I believe every attempt should be made to rule out other causes before one admits this to be the primary factor.

SPONTANEOUS SUBARACHNOID HEMORRHAGE

A Brief Review of Fifty Consecutive Cases
John Tucker, M.D.

As a rule, an attack of spontaneous subarachnoid hemorrhage is characterized by the sudden onset of severe suboccipital or parietal headache, dizziness, nausea, vomiting and somnolence or even coma. If a spinal puncture is done within the first week, one finds an even distribution of blood throughout the fluid and a definite elevation in intraspinal pressure. Unfortunately, this disaster is prone to occur in young adults, rather than in those individuals who have reached the degenerative period of life. Great importance should be attached to the proper diagnosis of the milder cases, particularly in its differentiation from migraine headaches. Recurrences of subarachnoid hemorrhage are the rule, particularly if the patient is not educated to live a quiet life, free from any physical or emotional strain. Even under the best of conditions, the patient usually dies of a second or third massive hemorrhage. While the exciting factor is mainly the increase of intravascular pressure brought about by lifting, straining at stool or emotional excitement, still a few cases in our series experienced the hemorrhage when lying quietly in bed.

Autopsy studies have shown that the vascular weakness is usually congenital in origin. At one or more points where the arteries of the circle of Willis give off branches, there may be an inadequate amount of muscle fibre in the media. As a result of this lack of strength, a small aneurysm forms which often, without any prodromal symptom, ruptures into the subarachnoid space. Unfortunately, these weak spots have no support from any surrounding tissue, so that one can never be certain that bleeding may not recur. It is true that other pathologic states are responsible for subarachnoid hemorrhage such as traumatic ruptures of thecal arteries secondary to skull fracture, infected emboli, blood dyscrasias with hemorrhagic diathiasis or intracerebral hemorrhages which communicate with a ventricle or which rupture into the subarachnoid space. As a rule, the intracerebral bleeding occurs in the later decades of life, and when it is accompanied by permanent paralysis or paresis, it constitutes the usual "stroke," while in spontaneous subarachnoid hemorrhage, any impairment in muscle power or in nerve function is usually transient.

Inasmuch as sudden hemorrhage into the subarachnoid space may occur without the dramatic picture of coma or convulsions, especially when the leakage is slight, we thought it would be worth while to review a small series of cases, especially from the standpoint of diagnosis. In this study we have considered the age of the patient, type of

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onset, previous known attacks of subarachnoid hemorrhage, the spinal fluid findings, special operative procedures and, as far as possible, the end results.

In an analysis of fifty consecutive cases of spontaneous subarachnoid hemorrhage, we have found, as have most other authors, that the preponderance of instances occur in the younger age groups. While the range was from thirteen to seventy years, the average age was 41.7 years. When taken by decades, there were three in the second, five in the third, thirteen in the fourth, twelve in the fifth, twelve in the sixth, four in the seventh, and one in the eighth. In the series, thirty-three, or 66 per cent, were below fifty years of age. Studies from other sources show approximately the same average age at onset^{1,2}.

The sex distribution was fairly even, there being twenty-nine men and twenty-one women. We must emphasize the fact that it is a disease of young adults and early middle life.

Prodromal symptoms occurred in eighteen of our cases, existing from one month to as long as ten years. In the main, these consisted of attacks of suboccipital and frontal headaches, often associated with disturbances of vision such as blurring, diplopia or sharp ocular pains. While many of these complaints had been diagnosed "migraine," yet in some of the more severe attacks there is reason to suspect that small subarachnoid hemorrhages had occurred, with only short periods of disability. In five patients, one previous attack had been verified by the discovery of bloody spinal fluid. In one of these cases, two hemorrhages had occurred six months and eighteen months prior to the massive bleeding which had brought him to the hospital. The other four had experienced one small hemorrhage six weeks, eight weeks, eighteen months and twenty-two months previously.

The symptoms that announced the hemorrhage were quite consistently those of a sudden rise in intracranial pressure associated with meningeal irritation. In 90 per cent of the subjects, the major complaint was a sudden, severe headache, usually suboccipital and either limited to this area or associated with retrobulbar or bi-temporal pain. At times the whole skull felt as if it would burst or the sensation was that of a violent blow on the head. Associated with the headache was severe vomiting in 72 per cent of the cases and in the others there was more or less severe nausea. The onset of coma appeared suddenly or gradually in 44 per cent. All cases considered here survived this first period of unconsciousness, but as will be seen later, many had recurrences of coma at a later date, without recovery of the conscious state.

There were many other symptoms of diagnostic importance among this group of fifty cases. Paralysis or paresis of an arm, a leg, one side of the face or one side of the body appeared in 58 per cent. These

JOHN TUCKER DEATHS UNDER OBSERVATION

	Age	Operation	Circumstances of Death	Post Mortem	
1.	35	Encephalogram. L.F. Craniotomy for hematoma.	1 day P.O.	Hematoma L. Frontal Lobe. S.A.H. L. ant. comm. art.	
2.	38	0	17th day.	0	
3.	57	0	Found dead in bed.	0	
4.	16	Sub. occip. crani- otomy. Tumor 4th ventricle.	Post-op.	S.A.H. Medullo- blastoma.	
5.	53	0	6th day—during spinal puncture.	S.A.H. Aneur. R. ant. comm. ar	
6.	48	0	5th day—2nd hemorrhage.	0	
7.	60	0	2nd day.	0	
8.	50	0	4th day—2nd hemorrhage.	S.A.H. Aneur. L. int. carotid.	
9.	29	0	8th day—2nd hemorrhage.	0	
10.	50	0	2nd day—2nd hemorrhage.	0	
11.	31	0	10 minutes following spinal puncture.	0	
12.	50	Encephalogram. Laminectomy T. 3-8. Comm. Hydro- ceph.	8 days P.O. 0		
13.	41	Enceph. R. fronto- par. hematoma. Craniotomy, muscle applied to aneurysm.	9 days P.O. S.A.H. R. mi cerebral hemo rhage.		
14.	7	0	2 months—2nd hemorrhage.	0	
15.	64	0	Pneumonia 20 days after hemor- rhage.	S.A.H. Aneurysm R. int. carotid. Broncho-pneu- monia.	
16.	43	0	3rd hemorrhage, 2 days.	0	
17.	48	0	4th day.	0	

L. ant. comm. art = left anterior communicating artery.

SPONTANEOUS SUBARACHNOID HEMORRHAGE

findings were transient except in one case in which an intracerebral hemorrhage, which produced hemiplegia, had ruptured through the cortex into the subarachnoid space. This condition was verified by autopsy. While generalized convulsions appeared in only 18 per cent of cases, in one of these the patient continued to have recurrent grand mal attacks.

Ocular disturbances are a fairly common finding in aneurysms of the circle of Willis. In the anterior communicating artery there may be pressure on the optic chiasm while in the posterior communicating artery, pressure may be exerted on the oculomotor or abducens nerve with paralysis and diplopia. These symptoms may be intensified at the time of the hemorrhage and at times even the sheath of the optic nerve is infiltrated with blood. In 44 per cent of our cases there appeared such abnormalities as homonomous hemianopsia, quadrant defects, retinal hemorrhages, retrobulbar neuritis and extra-ocular palsies. The ophthalmic examination was often unsatisfactory due to poor cooperation by the patient.

Elevated blood pressure was not an outstanding finding. raised in only 12 per cent and in these the range was between 160 systolic, 70 diastolic and 170 systolic, 120 diastolic. One-half of these hypertensive cases died while under observation. Inasmuch as spontaneous subarachnoid hemorrhage is due principally to the simple rupture of a weak spot in an artery of the circle of Willis, the degree of intravascular pressure may determine the time of hemorrhage. While persistent arterial hypertension is relatively infrequent in this disease, yet the effects of exertion are important. In twenty-nine cases, an accurate story was obtained of the precise activities at the time of the vascular accident. In thirteen, or 26 per cent, the patient was under physical strain such as heavy lifting, while in sixteen, or 32 per cent, the patient was at rest, either standing quietly, sitting or lying down. Obviously, the factor of effort only hastened the hemorrhage and yet, if life can be prolonged by mental and physical quietude, a rigid limitation of activity is well worth while.

The essential diagnostic procedure in spontaneous subarachnoid hemorrhage is the lumbar puncture. One or more spinal taps were made in all fifty cases. In 76 per cent the fluid was grossly bloody, and in these the pressure ranged between 150 and 700 mm. of water. The average pressure in this group was 364 mm. of water. In 18 per cent the fluid was xanthochromic and in these the pressure varied between 80 and 350 mm. water. In the three remaining cases the fluid was clear and colorless with pressures of 110, 120, and 205, respectively. If we accept the upper limit of normal pressure at 150 mm. to 200 mm. water, we find that, with few exceptions, the intraspinal pressure is raised. The hemorrhagic fluids were taken within the first three days of the illness, while

those of yellow color were secured five to eight days after bleeding had occurred. The colorless fluids were obtained ten days to three weeks after the onset.

Careful investigation has shown that xanthochromia begins three to four hours after a subarachnoid hemorrhage occurs and that the fluid is clear and colorless in twenty days, even in cases of large hemorrhage³. According to Brain¹, xanthochromia begins in a few hours, the yellow color reaches its greatest intensity in about a week and becomes colorless in fourteen to twenty-one days. He believes that the red blood cells disappear from the subarachnoid fluid in two to three days. In our experience, the time interval was somewhat longer. However, these observations emphasize the importance of an early diagnostic lumbar puncture.

If at this point we summarize the symptoms and physical signs characteristic of spontaneous subarachnoid hemorrhage, the picture is about as follows: If a man or woman, under forty-five years of age, who was previously in good health suddenly becomes dizzy, develops a severe suboccipital or frontal headache, vomits, collapses, is carried to bed in a stupor, one should suspect the advent of an acute subarachnoid hemorrhage. A bloody spinal fluid under high pressure, as recorded by a manometer, completes the diagnosis. Unfortunately, however, the syndrome is not always so clear cut. For instance, the patient may not have been in good health prior to the accident. Perhaps headaches, visual disturbances or neurasthenic symptoms have been troublesome. such instances the bloody spinal fluid may be due to a bleeding intracranial tumor or a rare case of hemorrhagic encephalitis. Likewise, if the amount of blood is small, if the neck is quite stiff, or a positive Kernig is present and high fever develops rapidly we may be dealing with a case of true meningitis. These possible diagnostic pitfalls make it necessary for us to have adequate laboratory facilities. Likewise various other diagnostic procedures may be required such as plain roentgenograms of the skull for possible intracerebral calcification. erosion of the clinoid processes of the sella or other evidences of vascular or neoplastic lesions.

In four of our series of cases an encephalogram was done even in the presence of bloody spinal fluid and the patients survived the ordeal. In one case, a tumor of the fourth ventricle was present in addition to the subarachnoid hemorrhage.

The treatment of this group of fifty cases consisted largely of symptomatic care with the maintenance of good comfort, nutrition and adequate fluids, together with repetition of the spinal punctures as often as necessary to keep the intracranial pressure below 150 mm. of water. The spinal taps were made with a full realization of the danger of the procedure. In only two cases we are reasonably certain that death resulted

SPONTANEOUS SUBARACHNOID HEMORRHAGE

from the spinal puncture. (See table 1.) One patient ceased respirations during the withdrawal of spinal fluid and the other died about ten minutes after this procedure. Therefore, in view of this hazard, it is necessary to reduce the pressure slowly and as often as twice a day in cases of rapid, massive bleeding. The risk is much greater if this procedure is neglected.

While the ultimate prognosis in cases of spontaneous subarachnoid hemorrhage is most discouraging, the only hope for the prolongation of life lies in early diagnosis, attempts to arrest bleeding by rest and sedatives and the control of intracerebral pressure by repeated spinal punctures. Dr. W. James Gardner, of the neurosurgical service, has in two cases attempted to strengthen the weakened spot in the artery at the base of the brain by encircling it with a bit of temporal muscle. However, in both instances the patient expired later during a second hemorrhage. Venesection of several hundred cc. of blood has also failed to correct continued subarachnoid bleeding. In general, simple medical measures have been more satisfactory than the use of the more complicated procedures.

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